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the imposition of different time criteria for testing the occurrence of a spike in accordance with the standards to indicate the onset of a cerebral disorder.

Regarding claims 2 and 3, one of ordinary skill in the art would have found it obvious to set the slope criteria for detecting bovine spongioform encephalitis or Alzheimer's disease because these diseases have distinct EEG waveforms detectable with the differentiator and comparators set forth in the Demetrescu device.

Demetrescu teaches the selectivity of comparator 116 eliminates the effect of random noise. One of ordinary skill in the art would have found it obvious to divide the EEG data series by two because Demetrescu further teaches short waves generated by random noise do not normally have a duration of six milliseconds and, accordingly, are discriminated in that they will not trigger the single shot 140.

Claims 4 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Demetrescu '697 in view of Skinner '294.

Demetrescu meets all of the claim limitations as discussed above except for using the data processing routine for the EEG data.

Skinner teaches using the data processing routine of claims 4 and 15.

One of ordinary skill in the art would have found it obvious to use the data processing routine of Skinner with the device of Demetrescu for processing the EEG data because Skinner teaches the algorithm is capable of analyzing EEG signals.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to George Manuel whose telephone number is (571) 272-4952.

George Manuel
Primary Examiner
Art Unit: 3762

11/13/05

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/767,861	SKINNER, JAMES
Examiner	**Art Unit**
George Manuel	3762

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date									
Final	Original	11/13/05									
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10767861

PLUS Search Results for S/N 10767861, Searched October 05, 2005

The Patent Linguistics Utility System (PLUS) is a USPTO automated search system for U.S. Patents from 1971 to the present. PLUS is a query-by-example search system which produces a list of patents that are most closely related linguistically to the application searched. This search was prepared by the staff of the Scientific and Technical Information Center, SIRA.

6201839	6444290	5517531	4070708
5709214	6448770	5533091	4121295
5720294	6469584	5537483	4256362
6886127	6807225	5566100	4328586
6377042	6137327	5608763	4354056
5840466	4339178	5729124	4388724
5963110	5673361	5779641	4453441
6263281	6137824	5799148	4494214
4613862	4791590	5917859	4501149
4633155	4806939	5933462	4550342
4782233	5249241	6236692	4573188
4816782	5278774	6245016	4594607
4831261	5297166	6411902	4605826
4881032	5375145	6477208	4755929
4882526	5396517	6819630	4766430
4905254	5465353	6868518	4813328
5019819	5511218	4631751	4835703
5182506	5526377	4885786	4838380
5197054	5559897	5831883	4843395
5254848	5631466	6078688	4853969
5272439	5642204	6263096	4885790
5276671	5661696	6366936	4894844
5295032	5693940	6166853	4901265
5363216	5745695	5442591	4901332
5376922	5818896	5654711	4953437
5390030	5875256	5742679	4972442
5392377	5887080	4276573	4975970
5410262	6111981	4312050	4987600
5566142	6266452	4323990	4991213
RE35561	6359878	4499594	5010524
5706115	6377607	4600904	5016104
5753413	6388532	5285167	5181032
5798728	6411978	5301027	5182558
5834085	6449594	5406284	5263120
6068739	6574567	5422643	5276614
6084480	5757909	5446758	5285478
6128359	5014185	5455839	5297063
6134198	5631501	5463575	5297065
6141297	5673004	5483238	5301134
6161077	5761302	5629701	5303309
6188289	6028932	5646350	5323336
6254964	6347144	5757299	5373455
6266210	6430430	5769384	5374892
6291052	6476034	5940019	5412587
6307400	5201321	5949374	5424653
6324035	5227972	6066980	5436188
6404605	4541275	6078868	5448169
6407892	5274739	6122619	5457719
6411658	5384560	6128597	5463720
6432563	5499399	6191730	5471527

ATTORNEY DOCKET NO. 22118.0002U2
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
James Skinner	:	Group Art Unit: 3736
Application No.: 10/767,861	:	Examiner: TBA
Filed: January 29, 2004	:	Confirmation No. 2987
For: "IMPROVED METHOD AND SYSTEM FOR DETECTING AND/OR PREDICTING CEREBRAL ANOMALIES"	:	

PRELIMINARY AMENDMENT

MAIL STOP MISSING PARTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NEEDLE & ROSENBERG, P.C.
Customer No. 23859

July 2, 2004

Sir:

Prior to the issuance of an Office Action pertaining to the above-identified patent application, please enter the following preliminary amendment and consider the following remarks.

Z25734

IN THE DRAWINGS

Please substitute the enclosed replacement drawing sheets (Sheets 1-7) for the ones which were filed with this application (Sheets 1-6), so that we may insert a correctly numbered sheet 4 between the drawings sheets currently numbered 3 and 4, and correctly renumber the subsequent drawing sheets.

PAGE 33/75 * RCVD AT 9/10/2008 2:07:00 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-6/6 * DNIS:2738300 * CSID:404 873 8501 * DURATION (mm-ss):09-40

REMARKS

The drawings are amended herein to include a total of seven drawing sheets. Copies of the correctly numbered replacement drawing sheets are enclosed herewith.

We are enclosing a copy of page 1 of the present application which was filed with the U.S. Patent and Trademark Office on January 29, 2004. Your attention is directed to the first paragraph, following the heading "Cross-Reference to Related Applications" in which it is stated:

> "This application is a Continuation-in-part of U.S. Utility Application No. 10/353,849 filed January 29, 2003. In addition, this application claims priority from U.S. Provisional Application No. 60/445,495 filed February 6, 2003. These applications are hereby incorporated by reference." (Emphasis added.)

While correctly numbered sheet 4 of the drawings was apparently omitted from the present Continuation-in-part application as filed, causing the remaining sheets to be incorrectly numbered, it formed a part of the application as filed. Specifically, sheet 4 was included in the parent application (Application No. 10/353,849) as filed on January 29, 2003. This correctly numbered sheet 4 is added by the present amendment, and no new matter is being added (given that the parent application has incorporated by reference).

For the foregoing reason, it is believed that this sheet 4 should be considered to be a part of this application and that no new matter has been added by this amendment. Accordingly, Applicant respectfully requests entry of same into the present application.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Gregory J. Kirsch
Registration No. 35,572

NEEDLE & ROSENBERG, P.C.
Customer No. 23859
678-420-9300
678-420-9301 (fax)

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service in an envelope addressed to: MAIL STOP MISSING PARTS, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on the date shown below.

Gregory J. Kirsch — Date: 2 JULY 2004

225734

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/767,861	01/29/2004	James Skinner	22118.0002U2

23859
NEEDLE & ROSENBERG, P.C.
SUITE 1000
999 PEACHTREE STREET
ATLANTA, GA 30309-3915

CONFIRMATION NO. 2987
FORMALITIES LETTER
OC000000012956021

Date Mailed: 06/15/2004

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit $ 385 to complete the basic filing fee for a small entity.
- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(e) of $65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121 are required. The drawings submitted are not acceptable because:
  - The drawing sheets do not have the appropriate margin(s) (see 37 CFR 1.84(g)). Each sheet must include a top margin of at least 2.5 cm. (1 inch), a left side margin of at least 2.5 cm. (1 inch), a right side margin of at least 1.5 cm. (5/8 inch), and a bottom margin of at least 1.0 cm. (3/8 inch).See Figures(s) 5A.

The applicant needs to satisfy supplemental fees problems indicated below.

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The required item(s) identified below must be timely submitted to avoid abandonment:

• Additional claim fees of **$18** as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$468** for a Small Entity

- **$385** Statutory basic filing fee.
- **$65** Late oath or declaration Surcharge.

• Total additional claim fee(s) for this application is **$18**

- **$18** for **2** total claims over 20.

Replies should be mailed to: Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

A copy of this notice MUST be returned with the reply.

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Initial Patent Examination Division (703) 308-1202
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ATTORNEY DOCKET NO. 22118.0002U2
EXPRESS MAIL LABEL NO. EL970609380US
Page 1 of 2

11324 U.S.PTO 012904

31353 U.S.PTO 10/767861 012904

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.: 22118.0002U2

First Inventor: James Skinner

Title: METHOD AND SYSTEM FOR DETECTING AND/OR PREDICTING CEREBRAL DISORDERS

Express Mail Label No.: EL970609380US

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility application contents

ADDRESS TO: Mail Stop PATENT APPLICATION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

1. ☒ Specification [Total Pages 30]
(Includes description, claims, and abstract)

2. ☒ Drawings [Total Sheets 6]

3. ☐ Oath or Declaration [Total Pages]
a. ☐ Newly executed (original or copy)
b. ☐ Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional) with Box 20B completed)

4. ☐ Application Data Sheet. See 37 CFR 1.76 [Total Pages ____]

5. ☐ Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
a. ☐ Computer Readable Form (CRF)
-OR-
☐ Statement under 37 CFR 1.821(e) (see Box 21 for statement)
b. ☐ Specification Sequence Listing on:
i. ☐ CD-ROM or CD-R (2 copies); or
ii. ☐ paper [Total Pages ____]
c. ☐ The contents of the computer readable form of the sequence listing and the sequence listing in the specification of the application are the same.

6. ☐ CD-ROM or CD-R in duplicate, large tables or Computer Program (Appendix)

ACCOMPANYING APPLICATION PARTS:

7. ☐ Copy of Assignment
8. ☐ 37 CFR 3.73(b) Statement (when there is an assignee)
9. ☐ Power of Attorney
10. ☐ English Translation Document (if applicable)
11. ☐ Information Disclosure Statement/PTO-1449
☐ Copies of IDS Citations [Total Citations ____]
12. ☐ Preliminary Amendment
13. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)
14. ☐ Nonpublication Request under 35 USC 122(b)(2)(B)(i) (Must attach form PTO/SB/35 or equivalent).
15. ☐ Authorization to Treat Reply Requiring Extension of Time as Incorporating Petition for Extension of Time
16. ☒ Return Receipt Postcard (MPEP 503)
17. ☐ Other: _____

18. The **FILING FEE** is calculated as follows: (Claims as filed, less any claims cancelled by Amendment)

Claims	Number Filed	Number Extra	Rate	$770.00 (Basic Fee)
Total claims	[22] – 20 =	2	X $18.00	$ 36.00
Independent claims	[2] – 3 =	0	X $84.00	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ 280.00	$
TOTAL OF ABOVE CALCULATIONS =				$816.00
☒ Applicant claims small entity status. See 37 CFR 1.27. Fees are reduced by ½.			–	$408.00
TOTAL FILING FEE =				$408.00

19. **Payment:**
☐ A check in the amount of $_____ is enclosed.
☐ Credit Card Payment Form PTO-2038 Authorizing Payment in the amount of $408.00 is enclosed.
☐ The Commissioner is hereby authorized to charge any additional amount due or credit any overpayment to Deposit Account No.

207465

20A. ☐ This application is an original application (not a continuation, divisional or continuation-in-part).

20B. ☒ This application is a ☒ continuation-in-part / ☐ continuation / ☐ divisional of prior Application No. 10/353,849.
The prior application was assigned to Examiner: TBA, Group Art Unit 3736.

☐ This application is a continuation or divisional application (not a continuation-in-part) that:
(i) names as inventors the same or fewer than all the inventors named in the prior application; and
(ii) contains no matter that would have been new matter in the prior application; and
(iii) a copy of the executed oath or declaration in the prior application, showing the signature or an indication thereon that it was signed:
☐ is enclosed.
☐ will follow.

☐ This application is a continuation or divisional application (not a continuation-in-part) that is being filed by less than all the inventors named in the prior application. In accordance with 37 C.F.R. §1.63(d)(2), the Commissioner is requested to delete the name(s) of the following person who are not inventors of the invention being claimed in this application:
_____

☐ This application is a continuation-in-part, continuation or divisional application naming an inventor not named in the prior application. A newly executed oath or declaration:
☐ is enclosed.
☐ will follow.

21. ☐ A sequence listing in computer readable form in compliance with 37 C.F.R. §§ 1.821-1.825 was submitted on _____ in prior Application No. _____, filed _____.
Pursuant to 37 C.F.R. § 1.821(e), applicant hereby requests that the computer readable form of the sequence listing submitted in the above-referenced prior application be used as the computer readable form of the sequence listing for the new application. The paper or compact disk copy of the Sequence Listing in the new application is identical to the computer readable copy filed in the prior application.

22. ☐ This application claims foreign priority benefits under 35 USC 119(a)-(d) or 365(b) of any foreign application(s) listed below, or under 35 USC 365(a) or 365(b) of any PCT application listed below.
Application No. PCT/US99/04990 Day/Month/Year Filed: March 5, 1999

23. Address all correspondence to the address associated with: CUSTOMER NO. 23859

Name of Attorney/Agent: Jennifer Pearson Medlin	Registration No.: 41,385
Signature:	Date: 1/29/04

Certificate of Express Mailing Under 37 C.F.R. § 1.10

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as Express Mail, Label No. EL970609380US, in an envelope addressed to: Mail Stop PATENT APPLICATION, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Michael Laird — 1/29/04 Date

207465

ATTORNEY DOCKET NO. 22118.0002U2

METHOD AND SYSTEM FOR DETECTING AND/OR PREDICTING CEREBRAL DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Continuation-in-part of U.S. Utility Application No. 10/353,849 filed January 29, 2003. In addition, this application claims priority from U.S. Provisional Application No. 60/445,495 filed February 6, 2003. These applications are hereby incorporated by reference.

BACKGROUND

The present invention is directed to a method and system for evaluating biological or physical data. More particularly, the present invention is directed to a system and method for evaluating biological or physical data for detecting and/or predicting cerebral disorders.

The recording of electrophysiological potentials has been available to the field of medicine since the invention of the string galvanometer. Since the 1930's, electrophysiology has been useful in diagnosing cardiac injury and cerebral epilepsy.

The state-of-the-art in modern medicine shows that analysis of R-R intervals observed in the electrocardiogram or of spikes seen in the electroencephalogram can predict future clinical outcomes, such as sudden cardiac death or epileptic seizures. Such analyses and predictions are statistically significant when used to discriminate outcomes between large groups of patients who either do or do not manifest the predicted outcome, but known analytic methods are not very accurate when used for individual patients. This general failure of known analytic measures is attributed to the large numbers of false predictions; i.e., the measures have low statistical sensitivity and specificity in their predictions.

It is usually known that something "pathological" is going on in the biological system under study, but currently available analytic methods are not sensitive and specific enough to permit utility in the individual patient.

The inaccuracy problems prevalent in the art are due to current analytic measures (1) being stochastic (i.e., based on random variation in the data), (2) requiring

stationarity (i.e., the system generating the data cannot change during the recording), and (3) being linear (i.e., insensitive to nonlinearities in the data which are referred to in the art as "chaos").

Many theoretical descriptions of dimensions are known, such as "D0" (Hausdorff dimension), "D1" (information dimension), and "D2" (correlation dimension).

D2 enables the estimation of the dimension of a system or its number of degrees of freedom from an evaluation of a sample of data generated. Several investigators have used D2 on biological data. However, it has been shown that the presumption of data stationarity cannot be met.

Another theoretical description, the Pointwise Scaling Dimension or "D2i", has been developed that is less sensitive to the non-stationarities inherent in data from the brain, heart or skeletal muscle. This is perhaps a more useful estimate of dimension for biological data than the D2. However, D2i still has considerable errors of estimation that might be related to data non-stationarities.

A Point Correlation Dimension algorithm (PD2) has been developed that is superior to both the D2 and D2i in detecting changes in dimension in non-stationary data (i.e., data made by linking subepochs from different chaotic generators).

An improved PD2 algorithm, labeled the "PD2i" to emphasize its time-dependency, has been developed. This uses an analytic measure that is deterministic and based on caused variation in the data. The algorithm does not require data stationarity and actually tracks non-stationary changes in the data. Also, the PD2i is sensitive to chaotic as well as non-chaotic, linear data. The PD2i is based on previous analytic measures that are, collectively, the algorithms for estimating the correlation dimension, but it is insensitive to data non-stationarities. Because of this feature, the PD2i can predict clinical outcomes with high sensitivity and specificity that the other measures cannot.

The PD2i algorithm is described in detail in U.S. Patents No. 5,709,214 and 5,720,294, hereby incorporated by reference. For ease of understanding, a brief description of PD2i and comparison of this measure with others are provided below.

The model for the PD2i is C(r,n,ref*,) ~ r expD2, where ref* is an acceptable reference point from which to make the various m-dimensional reference vectors, because these will have a scaling region of maximum length PL that meets the linearity (LC) and convergence (CC) criteria. Because each ref* begins with a new coordinate in each of the m-dimensional reference vectors and because this new coordinate could be of any value, the PD2i's may be independent of each other for statistical purposes.

The PD2i algorithm limits the range of the small log-r values over which linear scaling and convergence are judged by the use of a parameter called Plot Length. The value of this entry determines for each log-log plot, beginning at the small log-r end, the percentage of points over which the linear scaling region is sought.

In non-stationary data, the small log-r values between a fixed reference vector (i-vector) in a subepoch that is, say, a sine wave, when subtracted from multiple j-vectors in, say, a Lorenz subepoch, will not make many small vector-difference lengths, especially at the higher embedding dimensions. That is, there will not be abundant small log-r vector-difference lengths relative to those that would be made if the j-vector for the Lorenz subepoch was instead in a sine wave subepoch. When all of the vector-difference lengths from the non-stationary data are mixed together and rank ordered, only those small log-r values between subepochs that are stationary with respect to the one containing the reference vector will contribute to the scaling region, that is, to the region that will be examined for linearity and convergence. If there is significant contamination of this small log-r region by other non-stationary subepochs, then the linearity or convergence criterion will fail, and that estimate will be rejected from the PD2i mean.

The PD2i algorithm introduced to the art the idea that the smallest initial part of the linear scaling region should be considered if data non-stationarities exist (i.e. as they always do in biological data). This is because when the j-vectors lie in a subepoch of data that is the same species as that the i-vector (reference vector) is in, then and only then will the smallest log-r vectors be made abundantly, that is, in the limit or as data length becomes large. Thus, to avoid contamination in the correlation integral by species of data that are non-stationary with respect to the species the reference vector is

PAGE 41/75 * RCVD AT 9/10/2008 2:07:00 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-6/6 * DNIS:2738300 * CSID:404 873 8501 * DURATION (mm-ss):09-40

in, one skilled in the art must look only at the slopes in the correlation integral that lie just a short distance beyond the "floppy tail".

The "floppy tail" is the very smallest log-r range in which linear scaling does not occur due to the lack of points in this part of the correlation integral resulting from finite data length. Thus, by restricting the PD2i scaling to the smallest part of the log-r range above the "floppy tail," the PD21 algorithm becomes insensitive to data non-stationarities. Note that the D2i always uses the whole linear scaling region, which always will be contaminated if non-stationarities exist in the data.

FIG. 1A shows a plot of log C(r,n,nref*) versus log r. This illustrates a crucial idea behind the PD2i algorithm. It is only the smallest initial part of the linear scaling region that should be considered if data non-stationarities exist. In this case the data were made by concatenating 1200 point data subepochs from a sine wave, Lorenz data, a sine wave, Henon data, a sine wave, and random noise. The reference vector was in the Lorenz subepoch. For the correlation integral where the embedding dimension m=1, the segment for the floppy tail ("FT") is avoided by a linearity criterion of LC=0.30; the linear scaling region for the entire interval (D2i) is determined by plot length PL=1.00, convergence criterion CC=0.40 and minimum scaling MS=10 points. The species specific scaling region where the i- and j-vectors are both in the Lorenz data (PD2i) is set by changing plot length to PL=0.15 or lower. Note that at the higher embedding dimensions (e.g. m=12) after convergence of slope vs embedding dimension has occurred, the slope for the PD2i segment is different from that of D2i. This is because the upper part of the D2i segment (D2i-PD2i) is contaminated by non-stationary i-j vector differences where the j-vector is in a non-stationary species of data with respect to the species the i-vector is in.

This short-distance slope estimate for PD2i is perfectly valid, for any log-log plot of a linear region; it does not matter whether or not one uses all data points or only the initial segment to determine the slope. Thus, by empirically setting Plot Length to a small interval above the "floppy tail" (the latter of which is avoided by setting the linearity criterion, LC), non-stationarities can be tracked in the data with only a small error, an error which is due entirely to finite data length, and not to contamination by

PAGE 42/75 * RCVD AT 9/10/2008 2:07:00 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-6/6 * DNIS:2738300 * CSID:404 873 8501 * DURATION (mm-ss):09-40

non-stationarities.

Thus, by appropriate adjustments in the algorithm to examine only that part of the scaling region just above the "floppy tail", which is determined by, (1) the Linearity Criterion, LC, (2) the Minimum Scaling criterion, MS, and (3) the Plot Length criterion, PL, one skilled in the art can eliminate the sensitivity of the measure to data non-stationarities.

This is the "trick" of how to make the j-vectors come from the same data species that the i-vector is in, and this can be proven empirically by placing a graphics marker on the i- and j-vectors and observing the markers in the correlation integral. This initial part of the scaling region is seen mathematically to be uncontaminated only in the limit, but practically speaking it works very well for finite data. This can be proven computationally with concatenated data. When the PD2i is used on concatenated subepochs of data made by sine-, Lorenz-, Henon-, and other types of known linear and nonlinear data-generators, the short scaling segment will have vector-difference lengths made only by i- and j-vector differences that are stationary with respect to each other; that is, the errors for 1,200-point subepochs are found to be less than 5.0% from their values at the limit, and these errors are due to the finite data length, not scaling contamination.

FIG. 1B illustrates a comparison of the calculation of the degrees of freedom of a data series by two nonlinear algorithms, the Point Correlation Dimension (PD2i) and the Pointwise Scaling Dimension (D2i). Both of these algorithms are time-dependent and are more accurate than the classical D2 algorithm when used on non-stationary data. Most physiological data are nonlinear because of the way the system is organized (the mechanism is nonlinear). The physiological systems are inherently non-stationary because of uncontrolled neural regulations (e.g., suddenly thinking about something "fearful" while sitting quietly generating heartbeat data).

Non-stationary data can be made noise-free by linking separate data series generated by mathematical generators having different statistical properties. Physical generators will always have some low-level noise. The data shown in FIG. 1B (DATA) were made of sub-epochs of sine (S), Lorenz (L), Henon (H) and random (R)

mathematical generators. The data series is non-stationary by definition, as each sub-epoch (S, L, H, R) has different stochastic properties, i.e., different standard deviations, but similar mean values. The PD2i and D2i results calculated for the data are seen in the two traces below it and are very different. The D2i algorithm is the closest comparison algorithm to PD2i, but it does not restrict the small log-r scaling region in the correlation integral, as does the PD2i. This scaling restriction is what makes the PD2i work well on non-stationary data.

The PD2i results shown in FIG. 1B, using default parameters, (LC = 0.3, CC = 0.4, Tau = 1, PL = 0.15), are for 1,200 data-point sub-epochs. Each sub-epoch PD2i mean is within 4% of that known value of D2 calculated for each data type alone (using long data lengths). The known D2 values for S, L, H, and R data are, respectively, 1.00, 2.06, 1.26, and infinity. Looking at the D2i values, one sees quite different results (i.e., spurious results). Note that the D2i is the closest algorithm to PD2i, because it too is time-dependent. However, D2i it requires data stationarity, as does the D2 value itself. For stationary data, D2= D2i = PD2i. Only the PD2i tracks the correct number of degrees of freedom for non-stationary data. The single value of D2 calculated for the same non-stationary data is approximated by the mean of the D2i values shown.

For analysis by the PD2i, an electrophysiological signal is amplified (gain of 1,000) and digitized (1,000 Hz). The digitized signal may be further reduced (e.g. conversion of ECG data to RR interval data) prior to processing. Analysis of RR-interval data has been repeatedly found to enable risk-prediction between large groups of subjects with different pathological outcomes (e.g. ventricular fibrillation "VF" or ventricular tachycardia "VT"). It has been shown that, using sampled RR data from high risk patients, PD2i could discriminate those that later went into VF from those that did not.

For RR-interval data made from a digital ECG that is acquired with the best low-noise preamps and fast 1,000-Hz digitizers, there is still a low-level of noise that can cause problems for nonlinear algorithms. The algorithm used to make the RR-intervals can also lead to increased noise. The most accurate of all RR-interval detectors uses a 3-point running "convexity operator." For example, 3 points in a

running window that goes through the entire data can be adjusted to maximize its output when it exactly straddles an R-wave peak; point 1 is on the pre R-wave baseline, point 2 is atop the R-wave, point 3 is again on the baseline. The location of point 2 in the data stream correctly identifies each R-wave peak as the window goes through the data. This algorithm will produce considerably more noise-free RR data than an algorithm which measures the point in time when an R-wave goes above a certain level or is detected when the dV/dt of each R-wave is maximum.

The best algorithmically calculated RR-intervals still will have a low-level of noise that is observed to be approximately +/- 5 integers, peak-to-peak. This 10 integer range is out of 1000 integers for an average R-wave peak (i.e., 1% noise). With poor electrode preparation, strong ambient electromagnetic fields, the use of moderately noisy preamps, or the use of lower digitizing rates, the low-level noise can easily increase. For example, at a gain where 1 integer = 1 msec (i.e., a gain of 25% of a full-scale 12-bit digitizer), this best noise level of 1% can easily double or triple, if the user is not careful with the data acquisition. This increase in noise often happens in a busy clinical setting, and thus post-acquisition consideration of the noise level must be made.

There is thus a need for an improved analytic measure that takes noise into consideration. There is also a need for such a measure in the medical field, e.g., to detect biological anomalies, such as cerebral disorders.

SUMMARY

The objects, advantages and features of the present invention will become more apparent when reference is made to the following description taken in conjunction with the accompanying drawings.

According to exemplary embodiments, cerebral disorders are detected and/or predicted by analyzing input biological or physical data using a data processing routine. The data processing routine includes a set of application parameters associated with biological data correlating with the biological anomalies. The data processing routine uses an algorithm to produce a data series, e.g., a PD2i data series, which is used to detect or predict the onset of the biological anomalies.

According to one aspect of the invention, to reduce noise in the data series, the slope is set to a predetermined number, e.g., zero, if it is less than a predetermined value, e.g., 0.5.

According to another aspect, a noise interval within the data series is determined and, if the noise interval is within a predetermined range, the data series is divided by another predetermined number, e.g., 2, and new values are produced for the data series.

According to exemplary embodiments, reducing the noise in the data series improves detection/prediction of the onset of cerebral disorders, such as human prion diseases (Jacob-Creutzfeld Disease) and the various dementias (cardiovascular, traumatic, genetic), including Alzheimer's disease. The methods of the present invention can also be utilized to detect and predict the onset of bovine spongioform encephalitis, sheep scrapie and elk wasting disease.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A illustrates a plot of log C(r,n,nref*) versus log r for the conventional PD2i algorithm;

FIG. 1B illustrates a plot showing calculation of degree of freedom (dimensions) by two time-dependent algorithms when applied to noise-free non-stationary data;

FIGS. 2A and 2B illustrate performance of PD2i when low-level noise is added to the non-stationary data;

FIG. 3 illustrates examination of low-level noise in two sets of RR-intervals made from two digital ECG's;

FIGS. 4A-4F illustrate low level noise (insets) in the RR-intervals of control patients with acute myocardial infarctions;

FIGS. 4G-4L illustrate low level noise in the RR-intervals of arrhythmic death patients;

FIG. 5A illustrates an exemplary flow diagram for the logic of the NCA applied to ECG data in cardiology;

FIG. 5B illustrates an exemplary flow diagram for the logic of the NCA applied

to EEG data and related concepts in neurophysiology;

FIG. 6 illustrates exemplary flowcharts for the NCA implemented in software according to an exemplary embodiment;

FIG. 7 illustrates the PD2i of the heartbeats (RR) of a person with early dementia that was not confirmed until 10 years later compared to that of an age-matched normal subject; and

FIG. 8 illustrates the relationship of PD2i of the heartbeats (RR) in a cow with early and late stage bovine spongioform encephalitis (BSE).

DETAILED DESCRIPTION

According to an exemplary embodiment, a technique has been developed to eliminate the contribution of low-level noise to nonlinear analytic measures, such as PD2i.

To see why the noise is important, reference is made to FIGS. 2A and 2B. In FIGS. 2A and 2B, the data are the same S, L, H, and R data as described with reference to FIG. 1B. By definition, this data does not have any noise, as it is made by mathematical generators.

In FIG. 2A, ∀5 integers of low-level noise have been added to the non-stationary data series. The mean values of PD2i for each sub-epoch have not changed significantly, although there are a few large values out of the 1200 data points in each of the sub-epochs.

Adding noise of ∀14 integers, however, now results in spurious PD2i values, the means of which are all approximately the same, as shown in FIG. 2B.

According to exemplary embodiments, the NCA (noise consideration algorithm) examines the low level noise at high magnification (e.g., y axis is 40 integers full scale, x-axis is 20 heartbeats full scale) and determines whether or not the noise is outside a predetermined range, for example, whether the dynamic range of the noise is greater than ∀ 5 integers. If it is, then the data series is divided by a number that brings the noise back within the range of ∀ 5 integers. In this example, the data series may be divided by 2, as only the low-level bit of the 12 bit integer data contains the noise.

Since the linear scaling region of the correlation integral, calculated at embedding dimensions less than m = 12, will have slopes less than 0.5 when made from low-level noise (e.g., with a dynamic range of ∀5 integers), it is impossible to distinguish between low-level noise and true small slope data. Conveniently, since slopes less than 0.5 are rarely encountered in biological data, the algorithmic setting of any slopes of 0.5 or less (observed in the correlation integral) to zero will eliminate the detection of these small natural slopes, and it will also eliminate the contribution of low-level noise to the PD2i values. It is this "algorithmic phenomenon" that explains the empirical data and accounts for the lack of effect of noise within the interval between –5 and 5 when added to noise-free data (FIG. 2A). Noise of slightly larger amplitude, however, will show the noise-effects expected to occur with nonlinear algorithms (e.g., FIG. 2B).

Based on application to physiological data, it is now understood that the low-level noise must always be considered and somehow kept within a predetermined range, such as between ∀5 integers, or any other range that is a relevant one based on the empirical data. This consideration will prevent spurious increases of PD2i for low-dimensional data (i.e., data with few degrees of freedom) as illustrated by FIG. 2B. The proof of the concept lies in its simple explanation ("algorithmic phenomenon"), but perhaps even more convincing are the empirical data that support the use of an NCA. These data will now be presented.

The upper portion of FIG. 3 shows clinical RR-interval data from a patient who died of arrhythmic death (AD). A small segment of 20 heartbeats of the RR-interval data is magnified and shown at the bottom portion of FIG. 3. The linear regression represents the slow variation in the signal in the segment of data, while the up-and-down sawtooth variations represent the noise. Both ECG's and RR's appeared similar, but low-level observations of the data (20 heartbeats, 40-integer y-axis) revealed that one had data variation ranging between ±5 integers (OK) and the other between ±10 integers (too large). the larger-amplitude segment ("too large") is not identified and corrected, then the PD2i values would be spuriously larger, as in FIG. 2B. A consequence of such spuriously larger PD2i values is that a PD2i-based test might

make the wrong clinical prediction about the vulnerability of the patient's heart to lethal arrhythmogenesis.

According to exemplary embodiments, a larger-amplitude segment like that shown in FIG. 3 (too large) can be identified and corrected using the noise consideration algorithm (NCA).

Tables 1-4 show clinical data obtained as part of a study supporting the NCA concept. The goal of the study presented in Tables 1-4 was to predict the occurrence of arrhythmic death (AD) from a PD2i-test performed on the digital ECG of each patient. In a study of 320 patients exhibiting chest pain in the Emergency Room who were determined to be at high cardiac risk with the Harvard Medical School protocol, approximately one out of 3 patients needed application of the NCA to provide meaningful data. If the NCA had not been developed and applied, then the data obtained from these patients would have been meaningless in those cases where the low-level noise was too large.

Table 1A shows the contingency table of predictive AD outcomes (i.e., true positive, true negative, false positive, false negative) and the Relative Risk statistic (Rel) for the data set analyzed with several nonlinear deterministic algorithms (PD2i, DFA, 1/f-Slope, ApEn). Table 1B shows the contingency table of predictive AD outcomes and Rel for the data set analyzed with the more usual linear stochastic algorithms (SDNN, meanNN, LF/HF, LF(ln)).

Tables 1A and 1B show comparison of HRV algorithms in 320 high-risk patients (N) presenting chest pain in the Emergency Department and having assessed risk of acute-MI > 7%. All subjects had ECGs recorded and 12-month follow-up completed. The defined arrhythmic death outcomes are expressed as true or false predictions (T or F) by positive or negative HRV tests (P or N). Abbreviations in the tables are expressed as follows: SEN = sensitivity (%); SPE = specificity (%); REL = relative risk statistic; SUR = surrogate-rejection; OUT = outlier-rejection (>3 SD's); AF = atrial-fib rejection.

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Nonlinear Deterministic Algorithms:

PD2i≤1.4	PD2i>1.4	DFAOUT	DFA IN	1/fS≤-1.07	1/fS>-1.07	ApEn≤1	ApEn>1
TP = 19	TN = 140	TP = 6	TN = 52	TP = 6	TN = 158	TP = 4	TN = 166
FP = 96	FN = 1#	FP = 227	FN = 14	FP = 75	FN = 14	FP = 61	FN = 16
SEN = 95**	SUR = 65	SEN = 30	SUR = 15	SEN = 30	SUR = 65	SEN = 20	SUR = 65
SPE = 59**	OUT = 0	SPE = 19	OUT = 6	SPE = 68	OUT = 2	SPE = 73	OUT = 8
REL >>23**	N = 320	REL = 0.12	N = 320	REL = 0.91	N = 320	REL = 0.80	N = 320

Table 1A

Linear Stochastic Algorithms:

SDNN≤65	SDNN>65	MNN≤750	MNN>750	LF/HF≤1.6	LF/HF>1.6	LF(ln)≤5.5	LF(ln)>5.5
TP = 19	TN = 59	TP = 19	TN = 163	TP = 7	TN = 196	TP = 19	TN = 56
FP = 202	FN = 6	FP = 98	FN = 6	FP = 63	FN = 18	FP = 163	FN = 6
SEN = 76	AF = 29	SEN = 76	AF = 29	SEN = 28	AF= 29	SEN = 76	AF = 29
SPE = 23	OUT = 5	SPE = 62	OUT = 5	SPE = 76	OUT = 7	SPE = 37	OUT = 7
REL = 0.93	N = 320	REL= 4.57*	N = 320	REL = 1.19	N = 320	REL = 1.78	N = 320

Table 1B

** $p \leq 0.001$; Binomial Probability Test; with multiple-test alpha-protection (alpha level required is 8-fold smaller); expansion of $(P+Q)^n$ x 8-fold protection implies $p = 0.00016$, which is $p \leq 0.001$; also $p \leq 0.001$ by Fisher's Exact Test for row vs column associations in a 2 x 2 contingency table; all others are not significant by Binomial Probability Test.

* $p \leq 0.001$ Fisher's Exact Test only; i.e., not significant by Binomial Probability Test.

PD2i = Point Correlation Dimension (positive if minimum PD2i ≤ 1.4 dimensions, with a systematic low-dimensional excursion of more than 12 PD2i values); cases of randomized-phase surrogate rejections (SUR) were identical to the cases of $F_N \leq 33\%$.

DFA-OUT = Detrended Fluctuation Analysis (α_1 [short-term] is positive, if *out*side normal range of 0.85 to 1.15); randomized-sequence surrogate rejections (SUR).

1/f S = 1/f Slope (positive, if ≤ -1.075 for slope of log[microvolts^2 /Hz] vs log [Hz] integrated over 0.04 Hz to 0.4 Hz)

ApEn = Approximate Entropy (positive with cut-point ≤ 1.0 units, slope distance).

SDNN = Standard deviation of normal beats (positive, if ≤ 65 msec; for positive, if ≤ 50 msec, TP = 17).

MNN = Mean of normal RR-intervals (positive, if ≤ 750 msec).

LF/HF = Low frequency power (0.04 to 0.15 Hz)/high frequency power (0.15 to 0.4 Hz) (positive, ≤ 1.6).

LF(ln) = Low frequency power (0.04 to 0.15 Hz), normalized by natural logarithm (positive, ≤ 5.5).

This single AD patient died at 79 days and may not be a true FN; the digital ECG was recorded prior to two normal clinical ECGs, followed by a third positive one (i.e., the patient could be classified as an "evolving acute MI" who may have been TN at the time the ECG was recorded).

As can be seen from the data presented in Tables 1A and 1B, only the PD2i algorithm had statistically significant Sensitivity, Specificity, and Relative Risk statistics in this Emergency Room cohort.

Table 2 shows the Relative Risk statistic for various sub-groups of the high-risk cardiac patients. It is clear from the data presented in Table 2 that the PD2i performs best in all of them.

Table 2 shows the relative Risk for algorithmic prediction of arrhythmic death in 320 high-risk cardiac patients in the Emergency Room.

	AMI	Non-AMI	post-MI	non-post-MI
PD2i	7.39**	>12.17**	>4.51*	>16.85**
DFA	0.70	0.44	0.63	0.48
1/f Slope	1.67	0.56	0.87	0.90
ApEn	0.50	1.44	0.00	0.72
SDNN	0.68	1.75	0.83	1.34
MNN	1.94	>20.82**	3.00	3.61*
LF/HF	1.08	0.66	2.52	0.61
LF(ln)	1.08	>5.13*	0.73	2.09

Table 2

** $p \leq 0.001$, * $p \leq 0.05$, Fisher Exact Test for row vs column association in 2 x 2 contingency table; the > sign means that RR went to infinity because FN = 0; the value shown used FN = 1. Relative Risk = True Positive / False Negative x [True Negative + False Negative / True Positive + False Positive].

Table 3 shows performance of PD2i in the prediction of arrhythmic death in 320 high-risk cardiac patents in the Emergency Room, with and without the use of the NCA on the RR-interval data.

NCA USED		NCA NOT USED	
PD2i≤1.4	PD2i>1.4	PD2i≤1.4	PD2i>1.4
TP = 19	TN = 140	TP = 12	TN = 140
FP = 96	FN = 1#	FP = 96	FN = 8
REL >>23**	N = 320	REL = 1.8#	N = 320

Table 3

** $p<0.001$

Not statistically significant

Table 3 illustrates how the use or non-use of the NCA can change the study

outcome for the Relative Risk statistic. Without the consideration of the noise, the PD2i would not have had such remarkable predictive performance, and none of the other algorithms would have worked very well either.

Table 4 illustrates another PD2i measurement criterion that also works well in predicting AD. Table 4 shows the percentage of all PD2i values between 3 and 0 degrees of freedom (dimensions) for 16 arrhythmic death patients, each of whom died within 180 days of their ECG recording, and their matched controls, each of whom had a documented acute myocardial infarction, but did not die within 1-year of follow-up. The means of the two groups were highly statistically significant ($P < 0.0000001$, t-test).

Arrhythmic Death (within 180 days)		Matched Controls (AMI, no AD 1-yr)	
Patient ID	3<%PD2i>0	Patient ID	3<%PD2i>0
Bn032	95	Ct024-n	13
Bn078	90	Gr077-n	7
Bn100	90	Bn126	0
Bn090	90	Bn157	0
Bn113	70	Bn138	1
Bn137-n	90	Bn160	0
Bn159	98	Bn167	*3
Bn141-n	97	Ct001	0
Bn162	80	B216	0
Bn215-n	55	C002	5
Gr012	98	Bn220	1
Bn226-n	95	Ct005	6
Gr064	99	Ct008-n	0
B227	95	Ct022-n	0
Gr076	99	Ct009	1
Gr056-n	65	Gr047	5
Gr107	40	C021	0
Gr111	90	Gr090	0
Mean±SD	83±20**	Mean±SD	2.3±3.6**

Table 4

* These values were due to excessive ectopic beats that produced some scaling in the 3 to 0 range.

** P <0.000001, t-test; all AD subjects met PD2i<1.4 LDE and 0<PD2i>3.0 criteria; Sensitivity = 100%, Specificity = 100%

As can be seen from Table 4, in the high-risk ER patients who do not die (negative-test) the majority of their PD2i's are above 3 dimensions (degrees of freedom). In those patients who die (positive-test) the majority of their PD2i's are below 3 dimensions. This %PD2i<3 criterion completely separated the AD patients from their matched controls who had acute myocardial infarctions, but who did not die of AD (sensitivity = 100%; specificity = 100%). These results too are completely dependent upon the use of the NCA to keep the distributions from overlapping and the Sensitivity and Specificity at 100%. Those subjects in which the noise-bit was removed, that is, because the low-level noise in their RR-intervals was too high, are indicated by –n at the end of the file name.

PD2i Criteria for Predicting Arrhythmic Death

Each of the above Tables 1-4 was based on the observation of a low-dimensional excursion (LDE) to or below a PD2i of 1.4. That is, PD2i<1.4 was the criterion for prediction of AD. There were no false negative (FN) predictions using this criterion. The FN case is anathema to medicine, as the patient is told, "you are OK," but then he or she goes home to die of AD within a few days or weeks. False positive cases are expected in great numbers, as the cohort is a high-risk one having patients with acute myocardial infarctions, monomorphic ectopic foci, and other high-risk diagnoses. These positive-test patients are certainly at risk, and should be hospitalized, but they will not die, perhaps because of the drugs or surgical interventions that are applied in the hospital. In other words, the FP classification is not anathema to medicine. What is significant about the application of the PD2i to these ER patients is, 1) all AD's occurred in positive-test patients, and 2) 51% of the negative-test patients could be safely discharged from hospital, as none died within the year of follow-up. All of these clinical results are meaningful, but are completely dependent upon the use of the NCA to keep the Sensitivity and Specificity at 100% and the Relative Risk high.

FIGS. 4A-4L illustrate the PD2i<1.4 LED's and the %PD2i<3 criteria, both of which would have been changed significantly had the NCA not been used in some cases (NCA). Although they are related to one another, the use of both criteria in NCA examined data is probably the best and most universal way to predict AD among high-risk cardiac patients. This combination keeps statistical Sensitivity and Specificity at 100%, as seen for the AD patients and their acute MI controls (Table 4; FIGS. 4A-4L).

FIGS. 4A-4F illustrate low-level noise in the RR intervals of 6 acute myocardial infarction (acute MI) control patients, and FIGS. 4G-L illustrate low-level noise in the RR intervals of 6 arrhythmic death (AD) patients.

The long segment in each panel represents all of the RR-intervals in the 15 minute ECG. The short segment displays the low-level noise traces from a small 20 beat segment at a higher gain. Thus, in each panel, the noise is superimposed upon larger dynamic activity. All gains are the same for all subjects (long RR trace = 500 to 1000 integers; short RR trace = 0 to 40 integers).

Those subjects with a noise range judged to be larger than $\forall$ 5 integers (1 msec = 1 integer) had the noise consideration algorithm (NCA) performed before the PD2i was calculated. Thus, for example, the NCA was applied for the control subjects represented in FIGS. 4B, 4C, and 4F and for the AD subjects represented in FIGS. 4K and 4L.

The PD2i values corresponding to each RRi are displayed on a scale of 0 to 3 dimensions (degrees of freedom). For the AD subjects, as represented in FIGS. 4G-4L, there are many PD2i values less than 3.0. Table 4 shows this to be a mean of 83% of PD2i's below 3.0 for all subjects.

The predictability outcomes for the clinical data would not have been statistically significant without considering the noise content of the data. The NCA actually used in all of the above applications involved, 1) observing whether or not the dynamic range of the noise was outside a 10 integer interval, and then, if it was, 2) reducing the amplitude of the RR's sufficiently to get rid of the excess noise. The NCA was required in approximately 1/3 of the subjects. Rather than multiplying each data point by a value that would just reduce the dynamic range of the noise to under 10-

integers, the multiplier was 0.5 (i.e., it removed a whole bit of the 12-bit data).

All applications of NCA were done blinded to the data outcome (arrhythmic death was determined only after PD2i analyses with NCA were completed). This procedure excludes the possibility for experimenter bias and is a required design for statistical analyses.

According to an exemplary embodiment, the noise consideration algorithm as described above may be implemented in software. Determination of the noise interval may be made visually, based on data displayed, e.g., on a computer monitor. The data may be displayed at a fixed magnification, e.g., ∀ 40 integers full-scale centered around the mean of the segment displayed. If the values are outside the ±5 integer range, the user may decide to divide the data series by a predetermined value, or the division may occur automatically.

FIG. 5A illustrates an exemplary flow diagram for the logic of the NCA applied to ECG data. According to an exemplary embodiment, ECG from the subject is collected by a conventional amplifier, digitized, and then given as input to a computer for analysis. First, RR and QT intervals are made from the ECG data; then they are analyzed by the PD2i software (PD2-02.EXE) and QTvsRR-QT software (QT.EXE).

According to exemplary embodiments, the NCA is applied at two points, e.g., as part of the execution of the PD2i and QT vs RR-QT software and after execution of the PD2i and QT vs RR-QT software. For example, the NCA may be applied during execution of the PD2i and QT vs RR-QT software so that the slope of log c(n, r, nref*) vs. log r is set to zero if the slope is < than 0.5 and > than zero. Also, the NCA may be applied after execution of the PD2i and QT vs RR-QT software to divide the PD2i data series by a predetermined integer if the low-level noise is outside a predetermined interval, e.g., outside the interval between –5 and 5. If such division occurs, the PD2i calculation is repeated for the divided data by executing the PD2i and QT vs RR-QT software again.

After execution of the PD2i and QT vs RR-QT software is completed, the Point Correlation Dimension is then calculated as a function of time and displayed. The QT vs RR-QT plot is also made and displayed. Graphics Reports are then made for

assessing risk. The digitized ECG may be offloaded for storage.

The descriptions above relate largely to improving the detection/prediction of detecting deterministic low-dimensional excursions in non-stationary heartbeat intervals made from ECG data as a harbinger of fatal cardiac arrhythmias. The descriptions above also relate to improving the detection of dynamics of QT vs RR-QT jointly-plotted heartbeat subintervals, in a previously observed exclusion area, as harbingers of fatal cardiac dynamical arrhythmias. It will be appreciated, however, that the invention is also applicable to improving the detection/predication of other biological anomalies using, e.g., electroencephalographic (EEG) data. For example, the NCA may be applicable to improve the detection of persistent alterations in the deterministic dimensional reconstructions made from the non-stationary EEG data as a measure of altered cognitive state. The NCA may also be applicable to improve detection of an enlarged variance in the deterministic dimensional variations in EEG potentials as a harbinger of early paroxysmal epileptic activity.

FIG. 5B shows an exemplary implementation of the NCA algorithm for an epilepsy patient or normal subject undergoing neural analysis. EEG data from the subject is made by a conventional amplifier, digitized, and then given as input to a computer for analysis. The PD2i.exe software (PD2-02.exe) is then executed, setting the slope to, e.g., zero as necessary. Next, if the low-level noise is outside a predetermined interval, the PD2i data series is divided by a predetermined integer and the PD2i calculation is repeated for the divided data by executing the PD2i and QT vs RR-QT software again.

The Point Correlation Dimension is then plotted, and a Graphics Report is then made for assessing location of epileptic focii and/or alteration of cognitive state.

The NCA may be implemented on, e.g., a microcomputer. Although shown as separate elements, one or all of the elements shown in FIG. 5A and FIG. 5B may be implemented in the CPU.

Although the focus of the description above has been mainly on the assessment of ECG data and EEG data, it will be appreciated that other similar applications of the invention are possible. The source of the electrophysiological signal may be different,

and the structure of the graphics report(s) may be specific to the medical and/or physiological objectives. All analyses may use the PD2i algorithm and the NCA in some software form and may be accompanied by other confirmatory analyses.

The present invention also provides a method of detecting or predicting the onset of a cerebral disorder, comprising the steps of: analyzing input biological or physical data using a data processing routine including a set of application parameters associated with biological data correlating with the cerebral disorder to produce a data series, determining whether a slope of the data series is smaller than a predetermined value; if the slope is less than a predetermined value, setting the slope to a predetermined number; and using the data series to detect or predict the onset of the cerebral disorder.

FIG. 6 is a flow chart illustrating a process which the NCA may be implemented as software according to an exemplary embodiment. The flow begins with collection of the data. From the data, the i- and j-VECTORs are made and subtracted from one another (i-j DIFF). These vector difference lengths are entered, according the their value (X, 1 to 1000), into the MXARAY at the embedding dimension used (m, 1 to 12). The entry is made as an increment of a counter at each location of the MXARAY.

After completion of the making of the vector difference lengths, the counter numbers (3,7,9,8,2,6,7,4 . . .) are then used to make the correlation integrals for each embedding dimension; this is done by making a cumulative histogram as a function of X, at each m.sub.1, and then making the log-log plot of their cumulative values (e.g., PLOT log C (n,r) vs log r). The cumulative histogram results in the log-log data plotted in the correlation integral for each embedding dimension (m).

The correlation integral is then tested for five criteria. First, it is determined whether the slope at each m is less than 0.5. If the slope is less than 0.5, it is set to zero. Next, the longest linear scaling region that is within the linearity criterion (LC) is found. This is accomplished by examining each correlation integral by the LC to find the longest segment of the second derivative that falls within the limits of the set parameter (LC=0.30 means within a + to - deviation of 15% of the mean slope); this

iterative LC test will find a range above the "floppy tail" (i.e., the smallest log-r region that is unstable because of finite data length) and run up the correlation integral until the LC criterion is exceeded (bold section of top correlation integral).

Next, a determination is made whether the segment is within the plot length criterion (PL). If so, then the correlation integral scaling region is reset by the PL criterion; this value is set from the smallest data point in the correlation integral to its criterion value (e.g., 15%, bracket in second from top correlation integral). The upper and lower limits of this region are observed to see if they have at least the number of data points required by the minimum scaling (MS) criterion, e.g., 10. The selected regions of all correlation integrals (m-1 to m=12) are plotted and examined by the CC to see if convergence occurs at the higher embedding dimensions (e.g., m=9 to m=12); that is, to see if the selected regions have essentially the same slopes in which the standard deviation around the mean is within the limits set by the CC (.i.e., CC=0.40 means that the deviation around the mean is within + to - 20% of the mean value). If the CC criterion is passed, then the mean slope and standard deviation are stored to file and, e.g., displayed.

Finally, the low-level noise is examined by the user to test if the dynamic range is outside the –5 to +5 interval. If so, then the noise bit is removed from the data file (i.e., each data point value is divided by 2), and the modified file is then re-calculated, displayed, and stored.

If failure occurs at any of the early criteria (LC, PL, MS) within the flow, then the program will exit and move the PD2i reference vector to the next data point and then start all over. If failure occurs at the CC, the mean and standard deviation are saved without exiting, for it may be the case that later the CC is desired to be changed; i.e., the CC is a filter that determines whether or not the PD2i (i.e., the mean slope of m=9 to m=12) will be plotted in later graphical routines.

EXAMPLES

The present applicant has studied the degrees of freedom in HRV and found in humans with heart transplants (4) that the heartbeat variation was very regular and

hardly changed at all. The nonlinear analysis of the HRV in these transplant recipients indicated but 1.0 degree of freedom. In contrast, in normal subjects the variation was rich, with between 3 to 5 degrees of freedom. This result in the denervated heart suggests that it is the brain-projected neural activity to the heart that produces the HRV in the first place.

The nonlinear analysis of the heartbeat dynamics is a sensitive detector of underlying dynamics. It can clearly detect vulnerability to lethal arrhythmogenesis that other measures of HRV cannot (5). It can also detect alterations in the regulatory neurons when only the intrinsic cardiac nervous system is available to regulate the heartbeat intervals (6,7) or when higher cognitive systems involving the frontal lobes are involved (8).

HRV and Cognitive Function

The association of HRV and cognitive function and activity of daily living capacity in the elderly is not clear (9). The total power (i.e., LF and LF/HF ratio of the power spectrum) of HRV was found to be significantly lower in the dementia sub-group of the elderly subjects than in the normals (9). Therefore, it is not age per se that is related to the reduction in HRV. Rather, this result confirms the denervation study, which showed that it is the lack of higher neural activity projected to the heart that causes the HRV to diminish.

It is important to know at what point in progressive global neural challenge does the HRV actually begin to change. A change in the amplitude or oscillatory power of the variation, which comes with total neural involvement equivalent to descending nerve transsection, would be a late result and not very useful medically. Perhaps a more subtle change occurs early in the process that is picked up by a change in the degrees of freedom. It is quite likely that an early global challenge, as in the beginning stage of BSE and/or Alzheimer's disease, has an affect on a number of total neurons and thus the number of degrees of freedom of the HRV would become reduced significantly. If this is the case, then this nonlinear measure of HRV could be the harbinger of what is to result 10 years later in the disease process.

One elderly subject, SGW, was studied. This subject was in good health

(played tennis 3 times per week) and was not cognitively impaired. Although this subject had some minor difficulties in the recall of remote names (e.g., authors of various published manuscripts), there certainly was no sign of other short-term or long-term memory loss, or any indication of dementia. The HRV of this subject, however, was quite reduced at the time, to a value ranging between 2.0 and 1.0 dimensions. This reduction in nonlinear dimension (degrees of freedom) was clearly not the case in age-matched controls whose values ranged between 5 and 3 in the same range as that of other younger, normal subjects. The difference in mean PD2i values between SGW and the age-matched normal was highly statistically significant (t-test, $p<0.001$). The most important observation in this 10-year study was that after 10 years had passed, this particular subject (SGW) manifested a severe loss of short-term memory and exhibited severe dementia (Figure 7).

It is interpreted that tonic reduction in the degrees of freedom (dimension) of the HRV is a long-term predictor of the neural dementia to come. The same mechanism can be analogous for Bovine Spongioform Encephalitis detection in its early stages in cattle and similar prion diseases in humans (Jacob-Cruetzfeld Disease) that also take 10 years to develop.

The power spectra algorithm used to evaluate the HRV in previous studies presumes a linear stochastic model, which in turn requires that the variation in respiratory regulation be randomly distributed around a mean and be a stationary data series. Neither of these presumptions is valid in such physiological data series, as any behavior can interfere with respiration and produce nonlinear and non-stationary changes in the data.

Applicant has shown that a nonlinear algorithm, the Point Correlation Dimension (PD2i), which is based on a nonlinear deterministic model, addresses the problem of non-stationary data. It is able to accurately track the changes in the degrees of freedom of the variation in non-stationary data series (10). The power spectrum which was used in previous studies (1) requires data stationarity, and it was not likely to be present in the conscious behaving animals.

In application of the PD2i algorithm to clinical heart rate variability studies in

high-risk cardiac patients, the PD2i algorithm was markedly superior in its predictability of arrhythmic death outcome compared to other algorithms commonly used in the field (11,12), including the power spectrum.

The present invention shows that the PD2i reduction in the heartbeat variability in humans predicts progressive brain disorder in a case of cerebral dementia. This same nonlinear heartbeat measure can likewise predict progressive brain diseases in animals, especially cattle infected by bovine spongioform encephalitis. It has been shown that brain regulation of the heartbeats provides the higher dimensions of the PD2 (4). It is further disclosed that as the encephalitis progresses it can have a quantitative relationship with PD2i dimensional reduction (Figure 8). The same predictability can be used for early stage detection of other widespread cerebral disorders in humans, including, but not limited to, human prion diseases (Jacob-Creutzfeld Disease) and the various dementias (cardiovascular, traumatic, genetic), including Alzheimer's Disease. The technology can also work in similar or equivalent diseases in animals, including but not limited to, bovine spongioform encephalitis, sheep scrapie, elk wasting disease.

The reason the heartbeat interval variation encodes the physiological pathology to the initial stage of a progressive global disorders is because it measures the "cooperativity" (10) of the various afferent-efferent loops that compete to control the heartbeats. These afferent-efferent loops go all the way from the intrinsic nervous system wholly contained in the heart (6,7) to those that loop through the frontal lobes (8). Thus, the technology samples all levels of the central nervous system as well as the peripheral nervous system in the autonomic regulation of the heartbeats.

The inherent precision of the PD2i algorithm in quantitatively describing changes in the HRV is the result of it being based on a nonlinear deterministic model and treating the problem of data non-stationarity.

While the invention has been described with reference to specific embodiments, modifications and variations of the invention may be constructed without departing from the scope of the invention. For example, although the NCA has been described in its application to a PD2i data series, it should be appreciated that the NCA may also be useful in reducing noise in other types of algorithms, e.g., D2, D2i, or any other

predictive algorithm.

It should be understood that the foregoing description and accompanying drawings are by example only. A variety of modifications are envisioned that do not depart from the scope and spirit of the invention.

The above description is intended by way of example only and is not intended to limit the present invention in any way.

Throughout this application, various publications are cited. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art. The publications disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon.

PAGE 62/75 * RCVD AT 9/10/2008 2:07:00 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-6/6 * DNIS:2738300 * CSID:404 873 8501 * DURATION (mm-ss):09-40

ATTORNEY DOCKET NO. 22118.0002U2

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PAGE 63/75 * RCVD AT 9/10/2008 2:07:00 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-6/6 * DNIS:2738300 * CSID:404 873 8501 * DURATION (mm-ss):09-40

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WHAT IS CLAIMED IS:

1. A method of detecting or predicting a cerebral disorder, comprising the steps of:

analyzing input biological or physical data using a data processing routine including a set of application parameters associated with biological data correlating with the cerebral disorder to produce a data series,

determining whether a slope of the data series is smaller than a predetermined value;

if the slope is less than a predetermined value, setting the slope to a predetermined number; and

using the data series to detect or predict the onset of the cerebral disorder.

2. The method of claim 1, wherein the cerebral disorder is bovine spongioform encephalitis.

3. The method of claim 1, wherein the cerebral disorder is Alzheimer's disease.

4. The method of claim 1, wherein the data processing routine uses the following algorithm to produce a data series PD2i:

$$PD2i \subseteq \log C(n, r, nref^*)/\log r$$

where $\subseteq$ means scales as, C is the correlation integral for PD2i in which n equals the data length, r equals the scaling range, and nref* equals a location of the reference vector for estimating the scaling region slope of log C/log r in a restricted small log-r range that is devoid of the effects of non-stationary data.

5. The method of claim 1, wherein the predetermined value is approximately 0.5.

6. The method of claim 1, wherein the predetermined number is zero.

7. The method of claim 1, further comprising:

determining a noise interval within the data series; and

if the noise interval is within a predetermined range, dividing the data series by another predetermined number and repeating the step of analyzing to produce new values for the data series.

8. The method of claim 7, wherein the other predetermined number is two.

9. The method of claim 7, wherein the predetermined range is $-x$ to $+x$, where x is any number.

10. The method of claim 9, wherein the predetermined range is -5 to $+5$.

11. The method of claim 1, wherein the input biological or physical data includes electrophysiological data.

12. A method of detecting or predicting cerebral disorder, comprising the steps of:

analyzing input biological or physical data using a data processing routine including a set of application parameters associated with biological data correlating with the cerebral disorder to produce a data series;

determining a noise interval within the data series; and

if the noise interval is within a predetermined range, dividing the data series by a predetermined number and repeating the step of analyzing to produce new values for the data series; or

if the noise interval is outside the predetermined range, using the data series to detect or predict the onset of cerebral disorder.

13. The method of claim 12, wherein the cerebral disorder is bovine spongioform encephalitis.

14. The method of claim 12, wherein the cerebral disorder is Alzheimer's disease.

15. The method of claim 12, wherein the data processing routine uses the following algorithm to produce a data series PD2i:

$$PD2i \subseteq \log C(n, r, nref^*)/\log r$$

where $\subseteq$ means scales as, C is the correlation integral for PD2i in which n equals the data length, r equals the scaling range, and nref* equals a location of the reference vector for estimating the scaling region slope of log C/log r in a restricted small log-r range that is devoid of the effects of non-stationary data.

16. The method of claim 12, wherein the predetermined number is two.

17. The method of claim 12, wherein the predetermined range is $-x$ to $+x$, where x is any number.

18. The method of claim 17, wherein the predetermined range is -5 to $+5$.

19. The method of claim 12, further comprising:

determining whether a slope of the data series is smaller than a predetermined value; and

if the slope is less than a predetermined value, setting the slope to another predetermined number.

20. The method of claim 19, wherein the predetermined value is approximately 0.5.

21. The method of claim 19, wherein the other predetermined number is zero.

22. The method of claim 12, wherein the biological or physical data includes electrophysiological data.

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ABSTRACT

Cerebral disorders are detected and/or predicted by analyzing input biological or physical data using a data processing routine. The data processing routine includes a set of application parameters associated with biological data correlating with the biological anomalies. The data processing routine uses an algorithm to produce a data series, e.g., a PD2i data series. The data series is used to detect or predict the onset of the cerebral disorders. To reduce noise in the data series, the slope is set to a predetermined number if it is less than a predetermined value. To further reduce noise, a noise interval within the data series is determined and, if the noise interval is within a predetermined range, the data series is divided by another predetermined number, and new values are produced for the data series.

Inventor: James Skinner
Title: METHOD AND SYSTEM FOR DETECTING AND/OR PREDICTING CEREBRAL DISORDERS
Application No. TBA
Docket No. 22118.0002U2
Sheet: 1 of 6

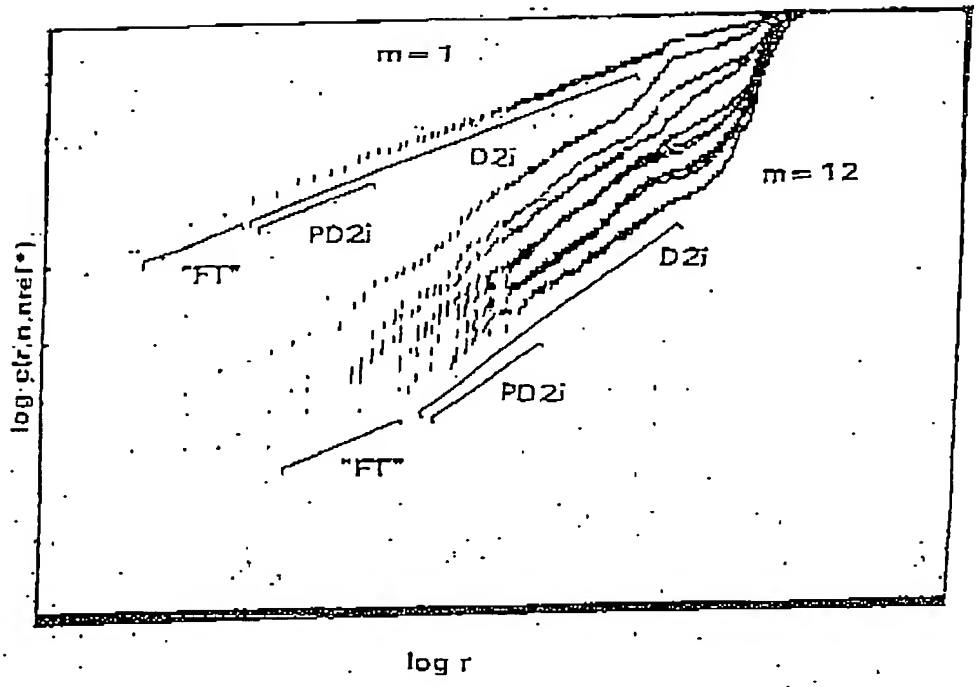

FIG. 1A

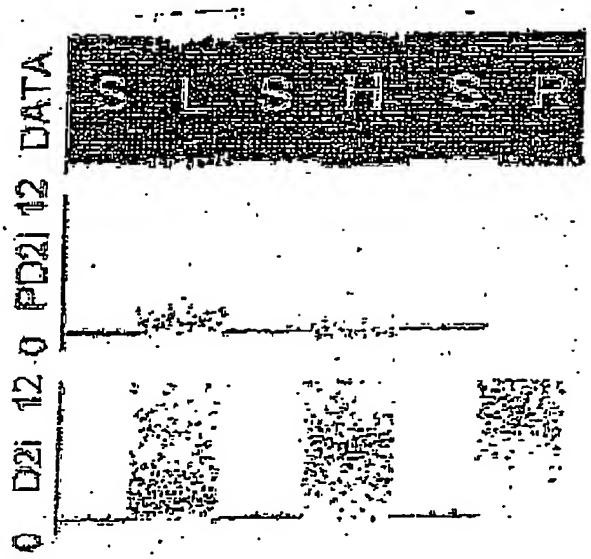

FIG. 1B

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Title: METHOD AND SYSTEM FOR DETECTING AND/OR PREDICTING CEREBRAL DISORDERS
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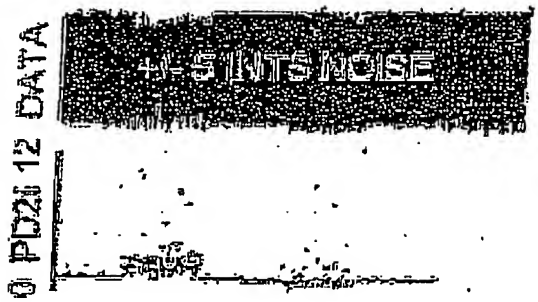

FIG. 2A

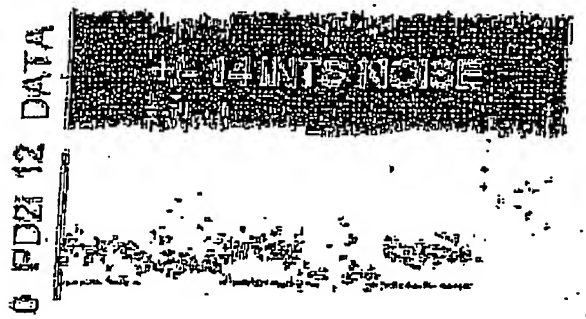

FIG. 2B

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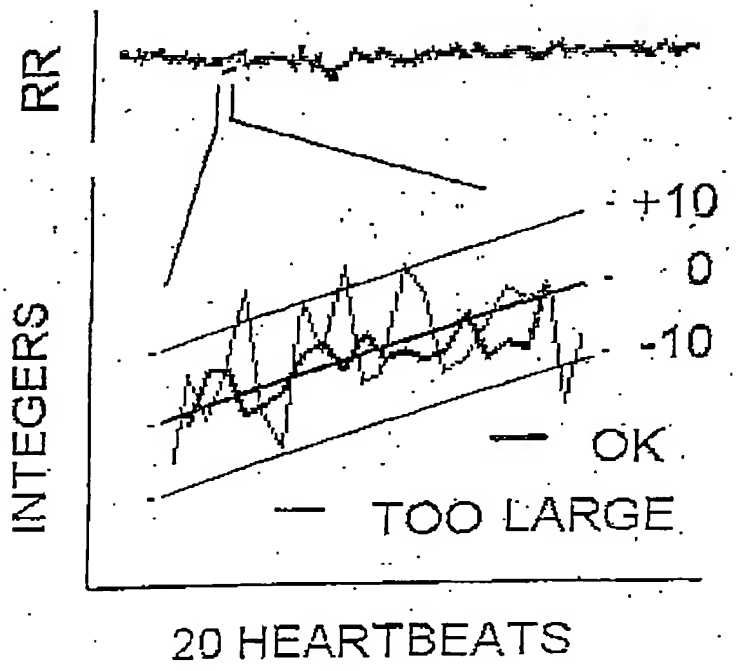

FIG. 3

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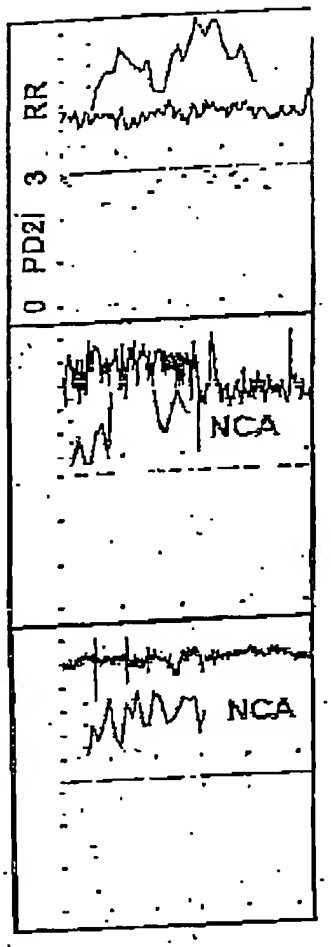

FIG. 4A

FIG. 4B

FIG. 4C

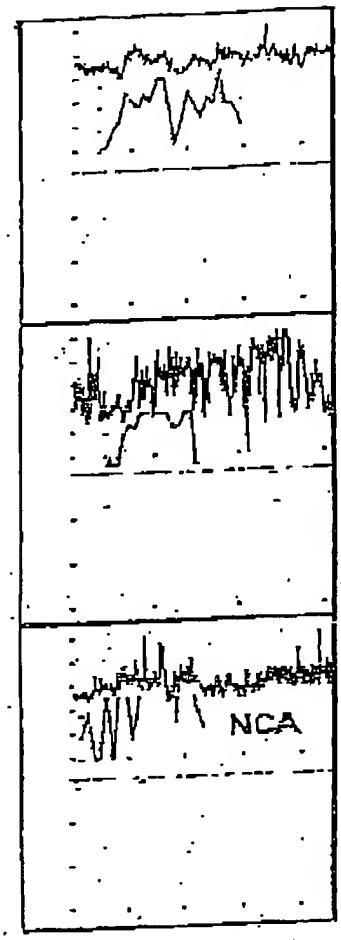

FIG. 4D

FIG. 4E

FIG. 4F

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Title: METHOD AND SYSTEM FOR DETECTING AND/OR PREDICTING CEREBRAL DISORDERS
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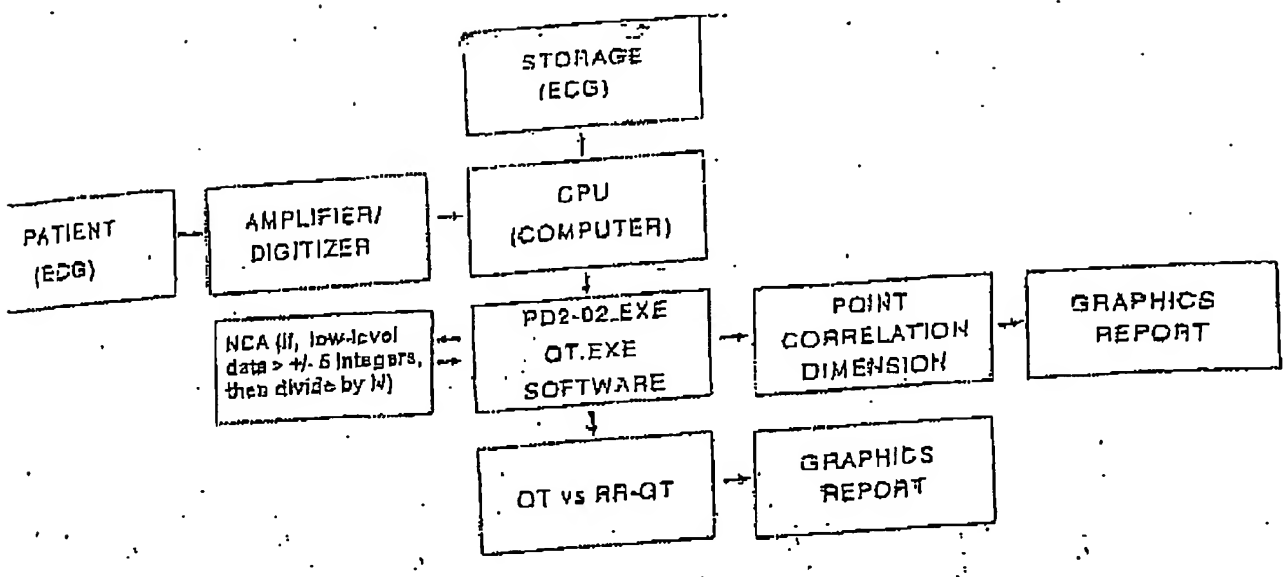

FIG. 5A

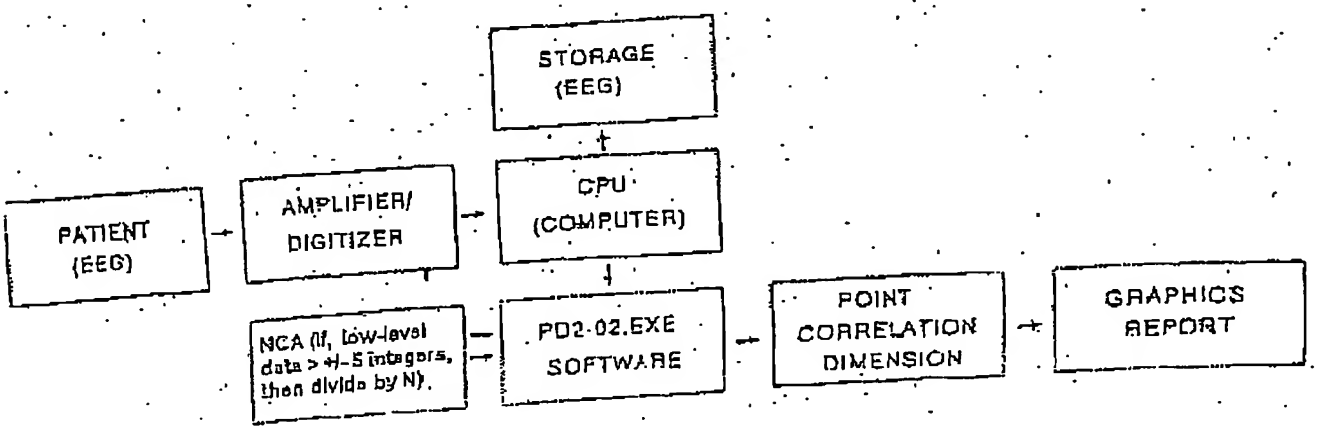

FIG. 5B

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Title: METHOD AND SYSTEM FOR DETECTING AND/OR PREDICTING CEREBRAL DISORDERS
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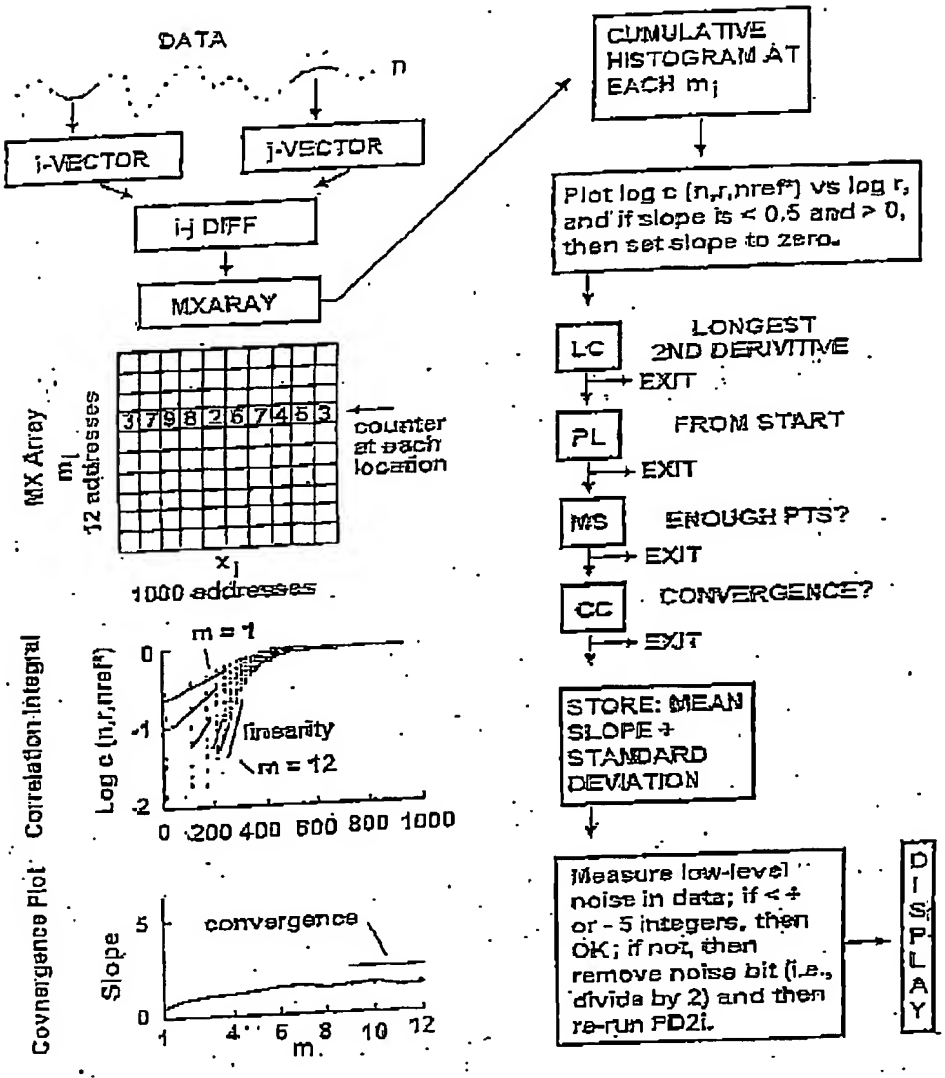

FIG 6

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Title: Method and System For Detecting And/Or Predicting Cerebral Disorders
Application No. TBA
Docket No. 22118.0002U2
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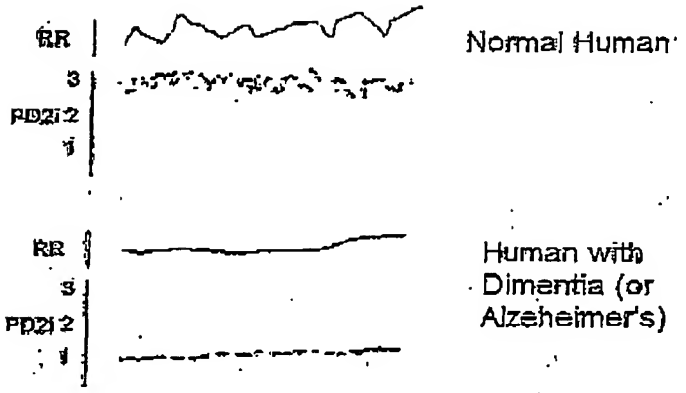

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FIGURE 7

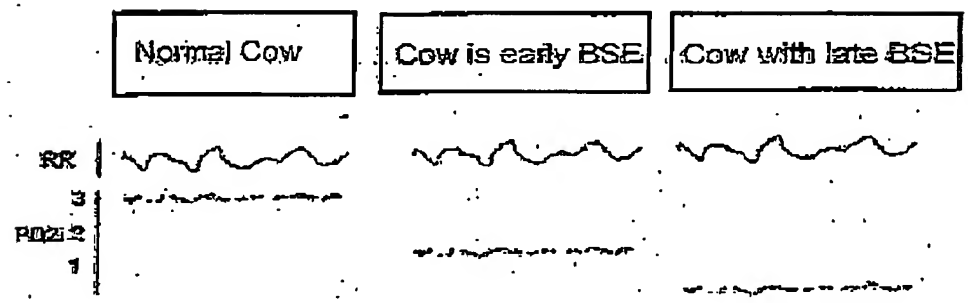

FIGURE 8

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PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2003

Application or Docket Number: 10767861

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	22	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	22 minus 20=	* 2
INDEPENDENT CLAIMS	2 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT	☐	

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	385.00	OR	BASIC FEE	770.00
X$ 9=	18.00	OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL	403.00	OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

ATTORNEY DOCKET NO. 22118.0002U2
APPLICATION NO. TBA

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

(X) Original ( ) Supplemental ( ) Substitute ( ) PCT

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original, first and sole inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled "IMPROVED METHOD AND SYSTEM FOR DETECTING AND/OR PREDICTING CEREBRAL ANOMALIES" which is described and claimed in the specification

(check one) [ ] which is attached hereto, or
[X] which was filed on January 29, 2004, as United States Application No. 10/767,861 and with amendments through (if applicable), or
[ ] in International Application No. PCT/, filed , and as amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information known by me to be material to the patentability of the claims of this application in accordance with Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code § 119 (a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) or § 365(b) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN APPLICATIONS: (ENTER BELOW IF APPLICABLE)			PRIORITY CLAIMED (MARK APPROPRIATE BOX BELOW)	
APP. NUMBER	COUNTRY	DAY/MONTH/YEAR FILED	YES	NO

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

APPLICATION NUMBER	FILING DATE

207648

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose all information known by me to be material to the patentability of the claims of this application as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION NO.	FILING DATE	STATUS (MARK APPROPRIATE COLUMN BELOW)		
		PATENTED	PENDING	ABANDONED
10/353,849	January 29, 2003		X	

I hereby appoint the practitioners at Needle & Rosenberg, P.C.,

Customer No.
23859

to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Address all telephone calls to Jennifer Pearson Medlin at telephone no. (678) 420-9300.

Address all correspondence to: Jennifer Pearson Medlin, Esq.

Customer Number
23859

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor: James Skinner

Inventor's signature: James E. Skinner Date: 2-9-04

Residence: 399 Autumn Drive, Bangor, PA 18013, U.S.A

Post Office Address: Same

Citizenship: United States of America

207648

ATTORNEY DOCKET NO. 22118.0002U2

METHOD AND SYSTEM FOR DETECTING AND/OR PREDICTING CEREBRAL DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Continuation-in-part of U.S. Utility Application No. 10/353,849 filed January 29, 2003. In addition, this application claims priority from U.S. Provisional Application No. 60/445,495 filed February 6, 2003. These applications are hereby incorporated by reference.

BACKGROUND

The present invention is directed to a method and system for evaluating biological or physical data. More particularly, the present invention is directed to a system and method for evaluating biological or physical data for detecting and/or predicting cerebral disorders.

The recording of electrophysiological potentials has been available to the field of medicine since the invention of the string galvanometer. Since the 1930's, electrophysiology has been useful in diagnosing cardiac injury and cerebral epilepsy.

The state-of-the-art in modern medicine shows that analysis of R-R intervals observed in the electrocardiogram or of spikes seen in the electroencephalogram can predict future clinical outcomes, such as sudden cardiac death or epileptic seizures. Such analyses and predictions are statistically significant when used to discriminate outcomes between large groups of patients who either do or do not manifest the predicted outcome, but known analytic methods are not very accurate when used for individual patients. This general failure of known analytic measures is attributed to the large numbers of false predictions; i.e., the measures have low statistical sensitivity and specificity in their predictions.

It is usually known that something "pathological" is going on in the biological system under study, but currently available analytic methods are not sensitive and specific enough to permit utility in the individual patient.

The inaccuracy problems prevalent in the art are due to current analytic measures (1) being stochastic (i.e., based on random variation in the data), (2) requiring

PAGE 23/75 * RCVD AT 9/10/2008 2:07:00 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-6/6 * DNIS:2738300 * CSID:404 873 8501 * DURATION (mm-ss):09-40

OIPE JC53 JUL 0 6 2004 PATENT & TRADEMARK OFFICE

Inventor: James Skinner
Title: METHOD AND SYSTEM FOR DETECTING AND/OR PREDICTING CEREBRAL DISORDERS
Application No. TBA
Docket No. 22118.0002U2
Sheet: 1 of 7

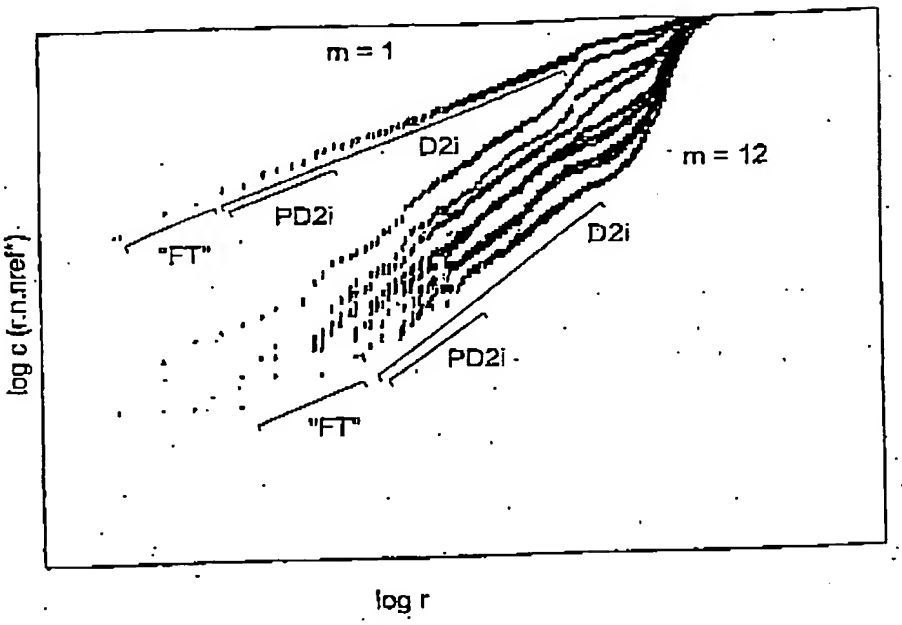

FIG. 1A

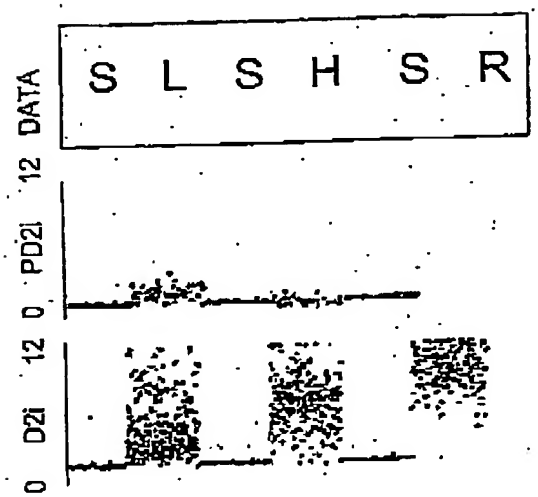

FIG. 1B

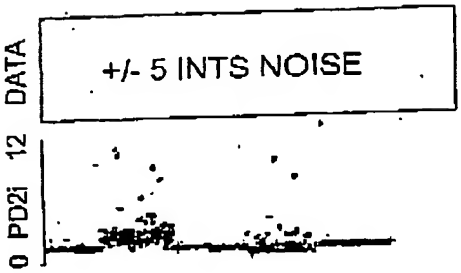

FIG. 2A

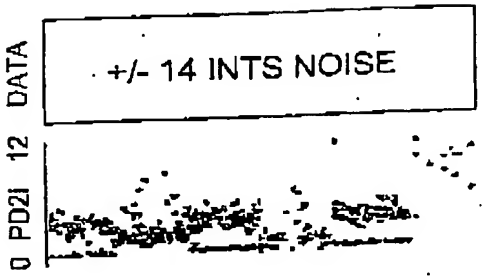

FIG. 2B

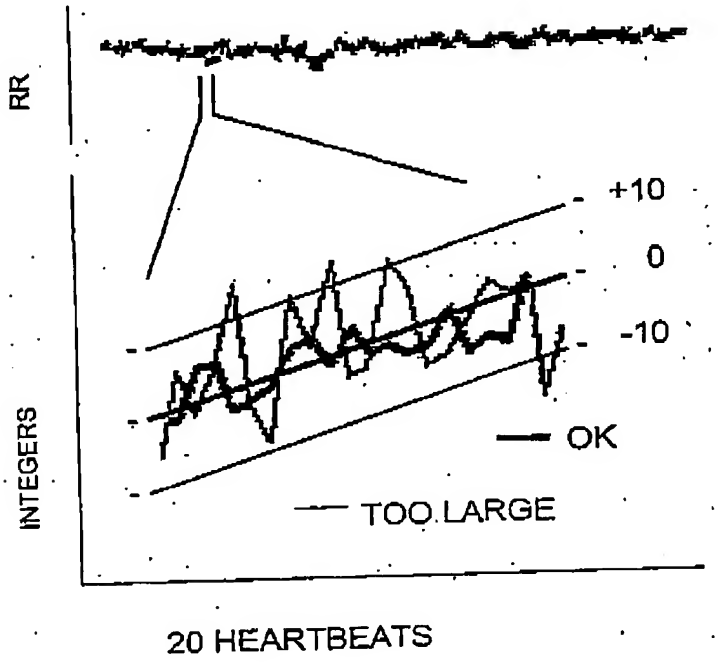

FIG. 3

Inventor: James Skinner
Title: Method And System For Detecting And/Or Predicting Cerebral Disorders
Application No. TBA
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FIG. 4A

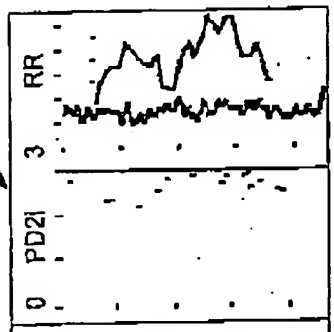


FIG. 4B

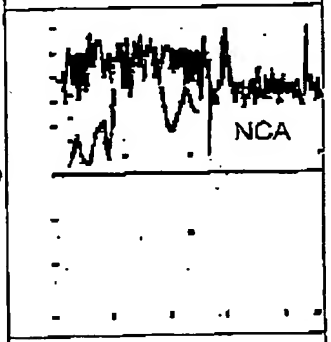


FIG. 4C

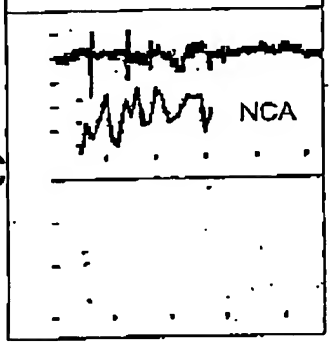


FIG. 4D

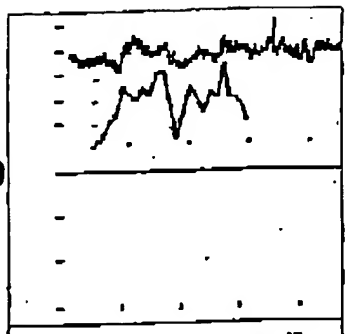


FIG. 4E

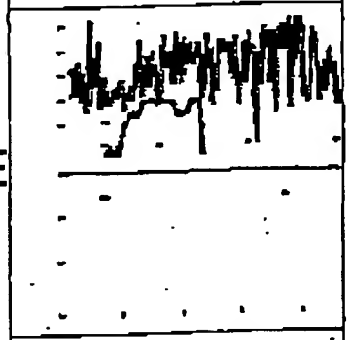
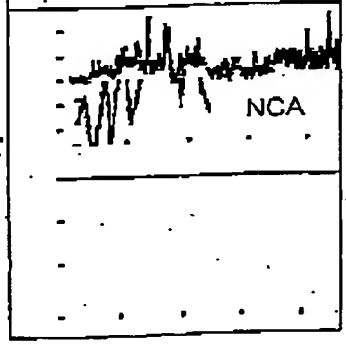


FIG. 4F



Inventor: James Skinner
Title: Method And System For Detecting And/Or Predicting Cerebral Disorders
Application No. TBA
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Sheet: 4 of 7

FIG. 4G

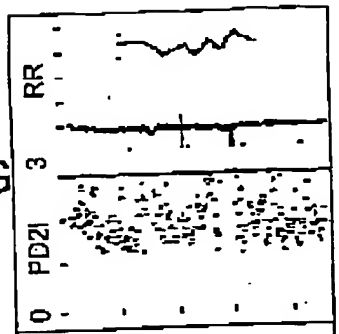


FIG. 4H

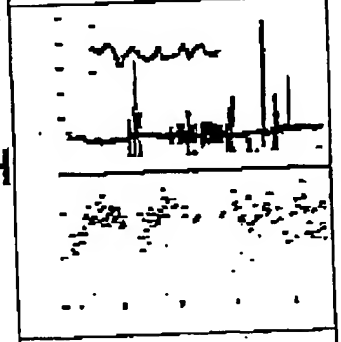


FIG. 4I

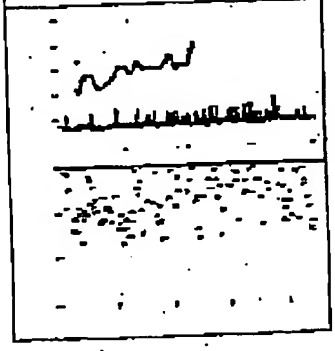


FIG. 4J

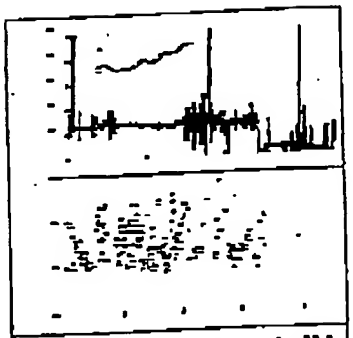


FIG. 4K

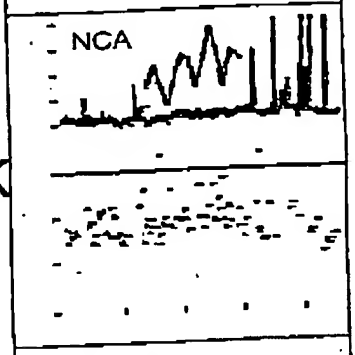
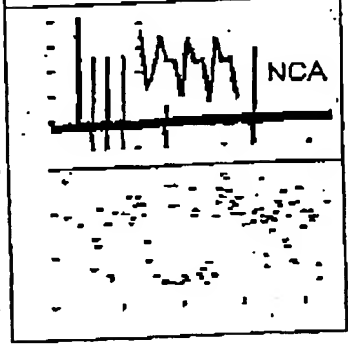


FIG. 4L



Inventor: James Skinner
Title: METHOD AND SYSTEM FOR DETECTING AND/OR PREDICTING CEREBRAL DISORDERS
Application No. TBA
Docket No. 22118.0002U2
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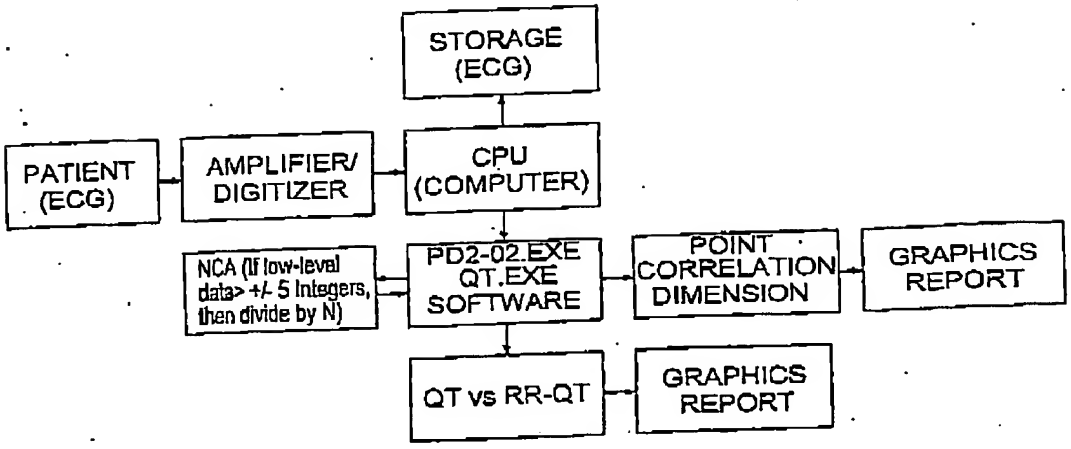

FIG. 5A

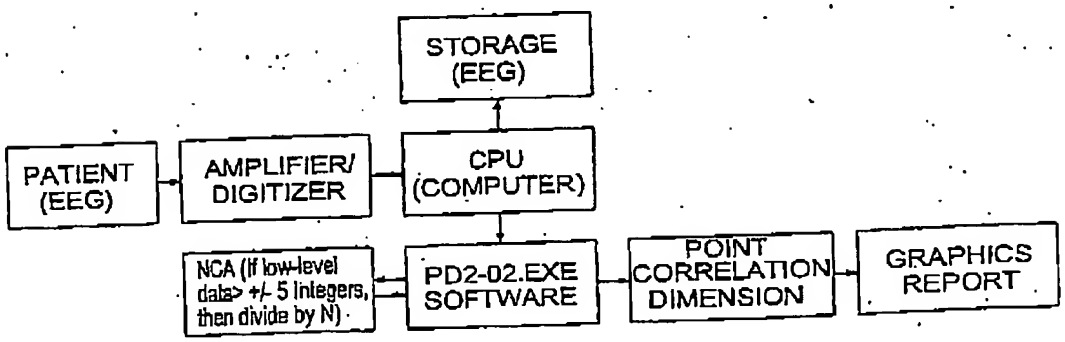

FIG. 5B

Inventor: James Skinner
Title: METHOD AND SYSTEM FOR DETECTING AND/OR PREDICTING CEREBRAL DISORDERS
Application No. TBA
Docket No. 22118.0002U2
Sheet: 6 of 7

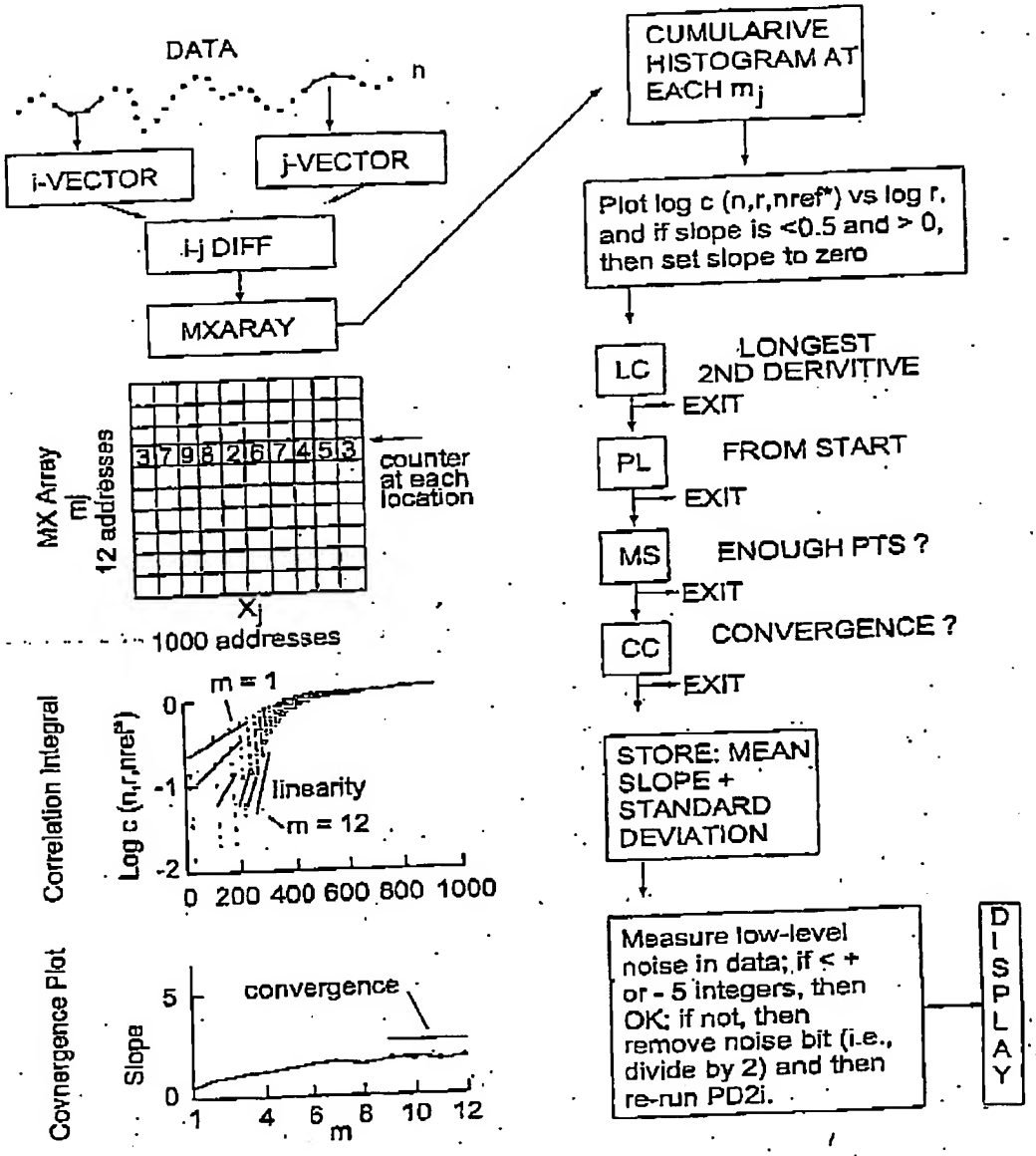

FIG. 6

Inventor: James Skinner
Title: Method And System For Detecting And/Or Predicting Cerebral Disorders
Application No. TBA
Docket No. 22118.0002U2
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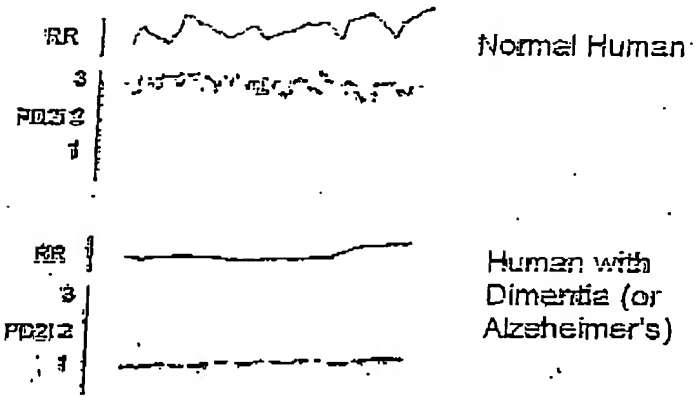

FIGURE 7

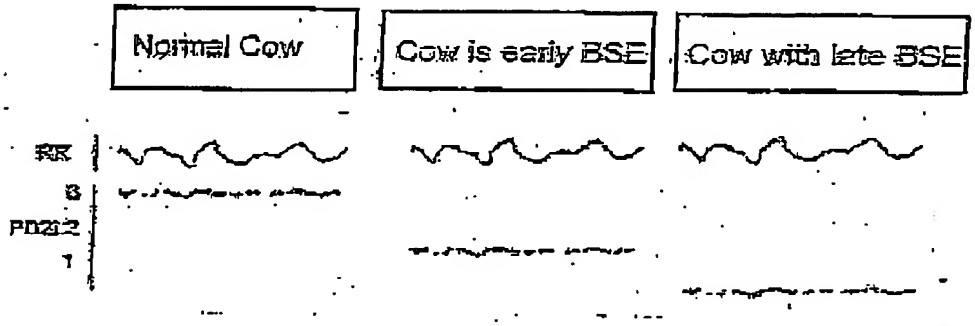

FIGURE 8

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PATENT
Page 1 of 2

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
James E. Skinner	)	Confirmation No. **2987**
	)	
Application No.: **10/767,861**	)	
	)	Group Art Unit: **3736**
Filed: **January 29, 2004**	)	
	)	
For: **"METHOD AND SYSTEM FOR DETECTING AND/OR PREDICTING CEREBRAL DISORDERS"**	)	Examiner: **TBA**

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NEEDLE & ROSENBERG, P.C.
999 Peachtree Street, Suite 1000
Atlanta, GA 30309

Sir:

Pursuant to the requirements of 37 C.F.R. § 1.56, submitted herewith on the accompanying Information Disclosure Statement List is a listing of documents known to Applicants and/or their attorneys. In accordance with 37 C.F.R. §1.98(a)(2), copies of any cited U.S. patent or U.S. patent application publication documents are not enclosed. Copies of any cited foreign patent document and/or any non-patent publication are enclosed.

This Information Disclosure Statement is believed to be filed in a timely manner pursuant to 37 C.F.R. § 1.97(b)(3), in that a first Office Action on the merits of the present patent application has not yet been mailed to Applicants.

Consideration of the cited documents and making the same of record in the prosecution of the above-referenced application are respectfully requested.

No fee is believed due; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Dawn V. Stephens, Registration No. 44,355

NEEDLE & ROSENBERG, P.C.
Customer No. 23859
999 Peachtree Street, Suite 1000
Atlanta, GA 30309-3915
(678) 420-9300 (Telephone)
(678) 420-9301 (Facsimile

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date show below.

CasSandra D. Belton

6/6/05
Date

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Modified Supplemental Form PTO-1449
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APPLICANT: James E. Skinner	
FILING DATE: January 29, 2004	GROUP: 3736

U.S. PATENT DOCUMENTS

EXAMINER INITIALS		DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	B1	5,482,045	1/09/96	Rust et al.			

FOREIGN PATENT DOCUMENTS

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER:	DATE CONSIDERED:

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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	APPLICANT: James E. Skinner	
	FILING DATE: January 29, 2004	GROUP: 3736

U.S. PATENT DOCUMENTS

EXAMINER INITIALS		DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
M	A1	5,720,294	02/24/98	Skinner			
M	A2	5,709,214	01/20/98	Skinner			

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OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

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	A4	"Is The Heart Preadapted To Hypoxia? Evidence From Fractal Dynamics Of Heartbeat Interval Fluctuations At High Altitude," Meyer *et al.*, *Integr. Physiol. Behav. Sci.*, 1998, Vol. 33, pp 9-40.
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	A13	"The Dimension of Chaotic Attractors," Farmer *et al.*, *Physica D*, Vol. 7D, Nos. 1-3, May, 1983, pp 153-180.
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M	A15	"Characterization of strange attractors," Grassberger *et al.*, *Physical Review Letters*, 1983, Vol. 50, No. 5, pp 346-349.

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	A16	"Direct Test for Determinism in a Time Series," Kaplan *et al.*, *Physical Review Letters*, 1992, Vol. 68, No. 4, pp 427-430.
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EXAMINER: G. Manuel	DATE CONSIDERED: 11/13/05

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LIST OF DOCUMENTS CITED BY APPLICANT
(Use several sheets if necessary)

ATTORNEY DOCKET NO.: 22118.0002U2	APPLICATION NO. 10/767,861
APPLICANT: James E. Skinner	
FILING DATE: January 29, 2004	GROUP: 3736

U.S. PATENT DOCUMENTS

EXAMINER INITIALS		DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
M	B1	5,482,045	1/09/96	Rust et al.			

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OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

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Notice of References Cited	Application/Control No. 10/767,861	Applicant(s)/Patent Under Reexamination SKINNER, JAMES	
	Examiner George Manuel	Art Unit 3762	Page 1 of 1

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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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PAGE 8/75 * RCVD AT 9/10/2008 2:07:00 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-6/6 * DNIS:2738300 * CSID:404 873 8501 * DURATION (mm-ss):09-40

Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
10/767,861	SKINNER, JAMES	
Examiner	Art Unit	
George Manuel	3762	

SEARCHED

Class	Subclass	Date	Examiner
600	509, 544, 545	11/13/2005	GM

INTERFERENCE SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)

	DATE	EXMR

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IFW

ATTORNEY DOCKET NO. 22118.0002U2
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
James E. Skinner	)	Confirmation No. 2987
	)	
Application No.:10/767,861	)	Group Art Unit: 3736
	)	
Filed: January 29, 2004	)	
	)	
For: "IMPROVED METHOD AND SYSTEM FOR DETECTING AND/OR PREDICTING CEREBRAL ANOMALIES	)	

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
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999 Peachtree Street
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July 28, 2004

Sir:

Pursuant to the requirements of 37 C.F.R. § 1.56, submitted herewith on the accompanying Form PTO 1449 is a listing of documents known to Applicants and/or their attorneys. All of the documents cited were cited by or submitted to the Patent Office in Application No. 10/353,849, filed January 29, 2003, to which the present application claims priority. Pursuant to 37 C.F.R. § 1.98(d), copies of these documents are not enclosed.

228949

This Information Disclosure Statement is believed to be filed in a timely manner pursuant to 37 C.F.R. § 1.97(b)(3), in that a first Office Action on the merits of the present patent application has not yet been mailed to Applicants.

No fee is believed due; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date show below.

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